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Marked Variation in Hepatic Steatosis in Metabolic Dysfunction-Associated Steatotic Liver Disease Over 5 Years: A Community-Based Study Using Controlled Attenuation Parameter

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Keywords: controlled attenuation parameter | hepatic steatosis | liver fat content | metabolic dysfunction-associated steatotic liver disease (MASLD) | steatotic liver disease | transient elastography

ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is very common and associated with significant morbidity and mortality due to its potential progression to cirrhosis and liver cancer. Whereas hepatic fat accumulation is the key to MASLD progression, little is known regarding changes in liver fat content over time in the general population. We aimed to investigate changes in liver fat in a longitudinal study of the general population.

Methods: We conducted a longitudinal study involving 195 randomly selected individuals from the general population, evaluated at two time points, 5 years apart. Participants with hepatic steatosis at baseline did not receive any specific treatment. The primary objective was to assess changes in liver fat content, as estimated by controlled attenuation parameter (CAP) using transient elastography. We also examined the frequency of steatosis resolution and development. CAP variability was assessed in two measurements 7 days apart in a cross-sectional study of 101 volunteers, with a mean variability of 9.9%. Steatosis resolution was defined as reduction of CAP > 10% from baseline with a final value < 275 dB/m, while steatosis development was defined as increase in CAP > 10% with a final value ≥ 275 dB/m.

Results: Remarkable variations in liver fat content were observed. Among the 88 participants with steatosis at baseline, 34% had resolution of steatosis (CAP decreased from 300 to 237 dB/m; $p < 0.001$). Resolution was associated with weight loss and reductions in transaminases and gamma-glutamyl transferase levels. In contrast, 29% of the 107 participants without steatosis at

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; GGT, gamma-glutamyl transpeptidase; IQR, interquartile range; LSM, liver stiffness measurements; MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; SLD, steatotic liver disease; SU, standard units of alcohol; T2DM, type-2 diabetes mellitus; TE, transient elastography.

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baseline developed it during follow-up. Increase in liver stiffness measurement (≥ 8 kPa) was associated only with persistent hepatic steatosis but not with steatosis resolution.

Conclusions: There is marked variation in liver fat content among participants from the general population over a period of 5 years, indicating its dynamic nature. These variations should be considered in epidemiological studies of MASLD.

1 | Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is the most common liver disease worldwide and its frequency is increasing in most countries of the world [1–3]. MASLD is strongly associated with metabolic risk factors such as obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension [4]. The clinical and epidemiological relevance of MASLD lies in its being a very common cause of cirrhosis and liver cancer, but it is well recognized that steatosis is a "sine qua non" condition for the development of inflammation and subsequent progression to liver fibrosis [5, 6].

Several studies have assessed the presence of steatosis in the general population and its relationship with inflammation and fibrosis in cross-sectional cohorts [7, 8]; however, there is a paucity of longitudinal studies evaluating changes in liver fat content in the general population. One of the reasons for this lack of studies is that liver fat is difficult to quantify using techniques that could be used in studies in the general population. Some studies have used liver ultrasound, but it only provides a semiquantitative measure of liver fat, which is not ideal for such studies. Magnetic resonance imaging proton density fat fraction (MRI-PDFF) is an excellent tool for evaluating liver fat and is considered the gold standard among the non-invasive tests but is typically restricted to hospital settings [9]. Finally, in the last few years, transient elastography (TE) with measurement of controlled attenuation parameter (CAP) has emerged as a very interesting and widely used method for non-invasive assessment of liver fat [10]. Although there have been many studies using CAP in the assessment of MASLD in hospital cohorts, there have been few reports on the use of CAP as a method for the assessment of steatotic liver disease (SLD) in the general population [11–13]. Previous studies have shown that the prevalence of SLD in the general population is between 30% and 40% and that its presence is associated with the presence of fibrosis in a significant percentage of participants [11, 14]. Nevertheless, there is a lack of information on the evolution of steatosis in participants from the general population.

2 | Materials and Methods

2.1 | Aims

The primary objective of the current study was to investigate changes in liver fat content, as assessed by CAP values, in a cohort of participants from the general population evaluated on two different occasions approximately 5 years apart. Secondary objectives were to investigate factors associated with either steatosis resolution or steatosis development and to assess whether changes in CAP values are associated with variations in liver stiffness measurements (LSM).

2.2 | Study Design and Population

This is a population-based longitudinal study of a cohort of participants from the community, previously reported to mensurate the prevalence of steatosis in the general population [11]. In the original cohort, participants were identified randomly from the registry of the primary care center and invited to participate. Exclusion criteria included pre-existing liver disease, active malignancy, severe chronic conditions, alcohol risk consumption (more than 21 standard units/week for males and more than 14 for females), and admission to nursing homes. The original cohort included 295 participants, 215 with and 80 without metabolic risk factors. All participants were contacted again after a median of 5 years from the first examination and 195 (66%) accepted to participate. Of the remaining 100 participants, 46 (16% of the overall cohort) could not be reached after multiple phone calls, 43 (14%) refused to participate, and 11 (4%) had died. The comparison of baseline characteristics between the participants who did and did not participate in the second examination is shown in Supporting Information S1: Table S1. Characteristics were similar except for an older age and higher prevalence of T2DM in the latter group. The second examination was identical to the first in that it included clinical data collection, anthropometric measurements, laboratory parameters, and a TE for CAP and LSM. The study protocol was approved by the Ethics Committee of Hospital Clínic de Barcelona (HCB/2015/0099), and all participants provided informed consent. The study complied with the principles of the Declaration of Helsinky and Spanish data protection regulations (article 9 of the UE legislation 2016/679).

2.3 | CAP and Liver Stiffness Measurements

TE was performed using standard procedures using the Fibroscan system (Fibroscan 502 Touch, Echosens, Paris, France), as described elsewhere [15]. All procedures in the second examination were performed by the same operator (MC) who was successfully trained and had performed more than 100 exams before the start of the study. Only examinations with at least 10 successful acquisitions, with an interquartile range/median (IQR/M) of LSM ≤ 30%, and with a success rate ≥ 60% were deemed valid.

2.4 | Evaluation of Variability of CAP Measurements

To assess the variability between two CAP measurements, we performed a cross-sectional study of 101 volunteers from the

Key Summary

- Summarise the established knowledge on this subject
  - Steatotic liver disease (SLD) is very prevalent among the general population and is associated with risk factors such as obesity and type-2 diabetes mellitus.
  - The presence of steatosis is a key factor for SLD progression, eventually leading to cirrhosis in some patients.
- What are the significant and/or new findings of this study?
  - In a cohort of participants from the general population evaluated two times 5 years apart, we found that 34% of participants with SLD had resolution of steatosis, while 29% of participants without SLD developed it during follow-up.
  - The resolution of steatosis was associated with a reduction in body weight and a decrease in transaminase and GGT levels.

community, aged 40 years or more, without known liver disease. In each subject, two measurements of CAP were performed by the same operator 7–10 days apart. Participants were instructed not to have any change in their lifestyle between the first and second examinations. Besides, participants were not informed of the results of the first measurement. Median (IQR) values of CAP in the first and second measurements were 236 (207–281) and 239 (208–274) dB/m, respectively ($p = 0.412$). There was a highly significant direct correlation between the first and second CAP measurements ($r = 0.83$; $p < 0.001$) (Supporting Information S1: Figure S1). The percent variability between the two measurements was 9.9 ± 7.4%, while the absolute variability was 11 ± 0.8 dB/m. Variability was lower in participants with high baseline CAP values (CAP ≥ 275 dB/m; $n = 24$) compared with those with low baseline CAP values (< 275 dB/m; $n = 77$), 5.8 ± 4.1% versus 11 ± 7.8%, respectively.

2.5 | Study Definitions

Hepatic steatosis was defined as a CAP value ≥ 275 dB/m, according to the EASL guidelines [16]. Steatosis resolution was defined as a decrease in the CAP value of greater than 10% in the second TE compared to the first TE with a second value < 275 dB/m. Steatosis development was defined as an increase in CAP value > 10% in the second examination compared to the first examination in participants without steatosis, with a second value ≥ 275 dB/m. The 10% variation in CAP values was chosen based on the findings of the variability study shown above. Increased LS was defined as an LSM > 8 kPa, according to EASL guidelines [16].

2.6 | Statistical Analysis

Statistical analyses were performed with standard statistical tests (Supporting Information S1: Methods) using SPSS 25 (SPSS Inc., Chicago, Illinois) and graphics were performed using Stata 16 (College Station, TX: StataCorp LLC). The significance level for all statistical tests was set at 0.05 two-tailed. There was no formal calculation of sample size because the current cohort derived from a previous cohort of participants identified randomly from the general population who were seen for a second visit 5 years after the index visit [11].

TABLE 1 | Characteristics of participants included in the first and second visits.

	First visit ($n = 195$)	Second visit[a] ($n = 195$)
Demographic and clinical		
Age (years)	61 (52–68)	66 (57–73)
Female	111 (57)	111 (57)
Weight (kg)	76.2 (66.4–86.1)	76.0 (65.8–87.5)
Waist circumference (cm)	100.0 (92.0–106.5)	102.0 (92.8–109.0)
BMI (kg/m^2)	29 (26–32)	28 (26–32)
Obesity (BMI ≥ 30 kg/m^2)	68 (35)	71 (36)
Overweight (BMI 25–29.9 kg/m^2)	81 (42)	83 (43)
Type 2 diabetes mellitus	32 (16)	39 (20)
Arterial hypertension	80 (41)	102 (52)
Dyslipidemia	102 (52)	115 (59)
Metabolic syndrome[b]	63 (33)	91 (48)
Biochemical profile		
Glucose (mg/dL)	94 (86–105)	90 (82–102)
Total cholesterol (mg/dL)	204 (177–229)	198 (170–220)
LDL-cholesterol (mg/dL)	128 (107–145)	123 (101–142)
HDL-cholesterol (mg/dL)	50 (42–62)	50 (41–60)
Triglycerides (mg/dL)	99 (76–146)	102 (84–156)
AST (U/L)	22 (19–27)	22 (19–28)
ALT (U/L)	23 (17–31)	21 (16–32)
GGT (U/L)	22 (16–35)	22 (17–32)
Glycated hemoglobin (%)	5.8 (5.5–6.3)	5.8 (5.5–6.3)
Transient elastography		
CAP (dB/m)	262 (225–300)	269 (227–311)
Liver stiffness (kPa)	4.4 (3.6–5.4)	4.3 (3.5–5.3)

Note: Values are median (IQR) or number of participants and percentages (in brackets).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; GGT, gamma glutamyltranspeptidase.
[a]Second visit was performed after a median of 5 years from the first visit.
[b]Metabolic syndrome was defined by the presence of 3 or more of the following features: a/waist circumference > 102 cm in men or > 88 cm in women; b/serum triglycerides > 150 mg/dL; c/high-density lipoprotein (HDL) cholesterol levels < 40 mg/dL in men or < 50 mg/dL in women; d/systolic blood pressure > 130 mmHg or diastolic blood pressure > 85 mmHg; and e/fasting plasma glucose > 110 mg/dL.

3 | Results

3.1 | Characteristics of the Study Population

Table 1 compares the characteristics of 195 participants in the first and second examinations. The majority were female with a mean age of 61 years at the first visit, and a large proportion exhibited metabolic risk factors for MASLD. The median CAP value was 262 dB/m, and 88 participants (45%) had steatosis (CAP value ≥ 275 dB/m). The median LSM value was 4.4 kPa, and 5 participants (3%) had a value ≥ 8 kPa. As expected, at the second visit, there was a slight but non-significant increase in the number of participants with metabolic risk factors, likely due to the increased age of participants. Overall, there were also no differences in mean LSM or CAP values between the first and second visits. Additionally, none of the participants reported alcohol risk consumption during the 5-year period.

3.2 | Longitudinal Changes in Liver Fat Content

There were remarkable changes in liver fat content between the first and second visits (Figure 1). Among the 88 participants with hepatic steatosis at the first visit, 30 (34%) had resolution of hepatic steatosis. In these participants, CAP decreased markedly from a median of 300 to 237 dB/m ($p < 0.001$). Individual CAP values in the first and second visits in this group are shown in Figure 2A. Notably, none of these participants underwent bariatric surgery or received pharmacological treatments known to reduce hepatic steatosis, such as GLP-1 agonists. Steatosis resolution was associated with a reduction in body weight, BMI, as well as transaminases and GGT levels, while no significant changes were observed in other parameters (Table 2). There were no significant changes in LSM (4.5 vs. 4.3 kPa, respectively, $p = 0.339$) in participants with steatosis resolution. By contrast, among the remaining 58 participants with steatosis at the first visit, CAP values increased significantly from 311 (IQR 289–343) to 330 (304–352) dB/m ($p = 0.015$), suggesting an increase in steatosis in most of them. In these participants, there was a significant increase in waist circumference from 105 (99–115) to 107 (100–114) cm ($p = 0.005$) and a trend for an increased frequency of risk factors of MASLD (data not shown). Out of these 58 participants, 5 (8.6%) had increased LSM (≥ 8 kPa) at baseline (31.6, 18, 10.1, 10, and 8.4 kPa) and 3 (5.2%) developed it during follow-up (LSM increased from 4.6, 4.9 and 6.1 to 12.2, 8.1, and 11.6 kPa, respectively).

Among the 107 participants without hepatic steatosis at the first visit, 31 (29%) developed hepatic steatosis during follow-up (Figure 1). In these participants, CAP values increased markedly from a median of 236 (211–247) to 304 (283–337) dB/m ($p < 0.001$) (Figure 2B). Steatosis development was associated with a significantly higher frequency of arterial hypertension and AST and glycated hemoglobin levels and a trend for an increase in waist circumference (Table 3).

In contrast, in the remaining 76 participants, CAP values increased only slightly from 223 (IQR 198–250) to 231 (206–256) dB/m ($p = 0.036$). Comparison of differences in the clinical and laboratory parameters between participants with resolution or development of steatosis is shown in Table 4. Resolution of steatosis was associated with a decrease in body weight and BMI, as well as reduction in transaminases, GGT, and glycated hemoglobin levels, and a trend for a decrease in waist circumference. There were no significant changes in LSM (4.6 vs. 4.9 kPa, respectively, $p = 0.569$).

4 | Discussion

The current study provides insight into the evolution of SLD due to MASLD in the general population. The main findings of the study are that in one third of participants with SLD related to MASLD, there was resolution of steatosis within a 5-year period. Conversely, approximately one third of participants without SLD but with metabolic risk factors developed steatosis within the same time frame. Therefore, a significant proportion of the general population exhibits marked variation in liver fat content over a 5-year period. Changes in liver fat are associated with corresponding changes in transaminases and GGT levels and

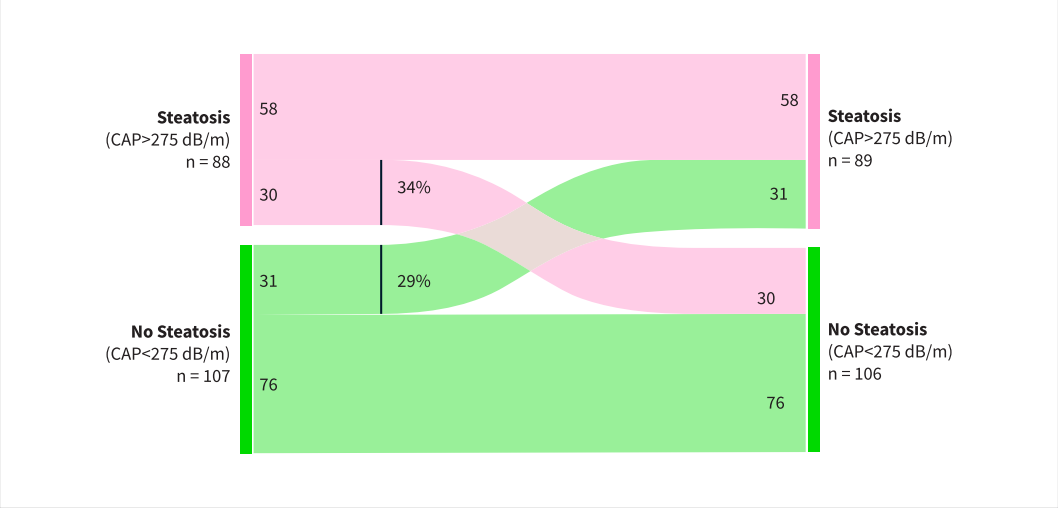

FIGURE 1 | Changes in hepatic steatosis: resolution and development of hepatic steatosis assessed by CAP.

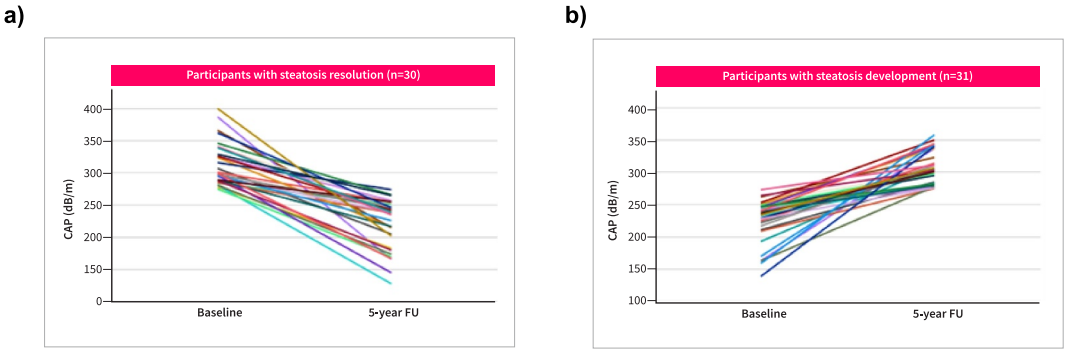

FIGURE 2 | (A) Individual values of CAP in participants with steatosis resolution. (B) Individual values of CAP in participants with steatosis development.

TABLE 2 | Characteristics of participants with steatosis resolution.

	First visit (n = 30)	Second visit[a] (n = 30)	p value
Demographic and clinical			
Age (years)	63 (57–69)	68 (62–74)	**< 0.001**
Female	14 (47)	14 (47)	1.000
Weight (kg)	73.2 (64.6–80.6)	69.8 (61.4–76)	**0.036**
Waist circumference (cm)	98 (92.5–102)	96 (90–104)	0.891
BMI (kg/m^2)	27.7 (24.5–29.6)	26.4 (23.6–28.0)	**0.037**
Obesity (BMI ≥ 30 kg/m^2)	8 (27)	3 (10)	0.125
Overweight (BMI 25–29.9 kg/m^2)	15 (50)	17 (57)	0.754
Type 2 diabetes mellitus	7 (23)	7 (23)	1.000
Hypertension	12 (40)	16 (53)	0.125
Dyslipidemia	18 (60)	19 (63)	1.000
Metabolic syndrome[b]	8 (27)	15 (50)	0.065
Biochemical profile			
Glucose (mg/dL)	97 (92–115)	95 (87–108)	0.061
Total cholesterol (mg/dL)	205 (186–240)	194 (167–221)	0.128
LDL-cholesterol (mg/dL)	129 (113–148)	125 (99–142)	0.121
HDL-cholesterol (mg/dL)	49 (40–59)	48 (41–61)	0.530
Triglycerides (mg/dL)	122 (93–174)	115 (84–160)	0.202
AST (U/L)	23 (20–27)	21 (19–26)	**0.026**
ALT (U/L)	24 (18–33)	21 (15–30)	**0.012**
GGT (U/L)	27 (21–36)	23 (16–30)	**0.018**
Glycated hemoglobin (%)	5.7 (5.3–6.4)	5.6 (5.2–6.6)	0.579
Transient elastography			
CAP (dB/m)	300 (289–339)	237 (182–251)	**< 0.001**
Liver stiffness (kPa)	4.5 (4.0–6.3)	4.3 (3.6–5.1)	0.339

Note: Values are median (IQR) or number of participants and percentages (in brackets). Blood values represent standard clinical parameters: glucose, lipid profile, and glycated hemoglobin (metabolic status), and AST, ALT, and GGT (liver function tests). Bold values indicate statistically significant differences ($p < 0.05$).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; GGT, gamma glutamyltranspeptidase.
[a]Second visit was performed after a median of 5 years from the first visit.
[b]Metabolic syndrome was defined by the presence of 3 or more of the following features: a/waist circumference > 102 cm in men or > 88 cm in women; b/serum triglycerides > 150 mg/dL; c/high-density lipoprotein (HDL) cholesterol levels < 40 mg/dL in men or < 50 mg/dL in women; d/systolic blood pressure > 130 mmHg or diastolic blood pressure > 85 mmHg; and e/fasting plasma glucose > 110 mg/dL.

appear to be driven mainly by modifications in body weight, although the participation of other risk factors cannot be ruled out.

Several studies have shown that CAP values have a good correlation with steatosis measured either histologically or by MRI-PDFF in cohorts of patients with SLD due to MASLD [17–19].

TABLE 3 | Characteristics of participants who developed hepatic steatosis during follow-up.

	First visit (n = 31)	Second visit[a] (n = 31)	p value
Demographic and clinical			
Age (years)	61 (52–66)	67 (57–72)	**< 0.001**
Female	20 (65)	20 (65)	1.000
Weight (kg)	79.3 (68–95.1)	81.2 (72.2–93.3)	0.206
Waist circumference (cm)	100 (92–110)	107 (96.8–112)	0.074
BMI (kg/m^2)	29.9 (26.1–32.5)	29.4 (26.6–35)	0.122
Obesity (BMI ≥ 30 kg/m^2)	15 (48)	14 (42)	1.000
Overweight (BMI 25–29 kg/m^2)	11 (36)	13 (45)	0.250
Obesity or overweight	26 (84)	27 (87)	1.000
Type 2 diabetes mellitus	6 (19)	7 (23)	1.000
Hypertension	11 (36)	17 (55)	**0.031**
Dyslipidemia	11 (36)	15 (48)	0.289
Metabolic syndrome[b]	11 (36)	14 (45)	0.508
Biochemical profile			
Glucose (mg/dL)	93 (87–110)	89 (81–99)	0.245
Total cholesterol (mg/dL)	208 (186–236)	214 (190–221)	0.791
LDL-cholesterol (mg/dL)	129 (115–143)	136 (119–144)	0.894
HDL-cholesterol (mg/dL)	50.00 (44–66)	53 (48–62)	0.845
Triglycerides (mg/dL)	101 (74–147)	102 (88–130)	0.688
AST (U/L)	20 (17–24)	22 (17–26)	**0.027**
ALT (U/L)	20 (15–24)	20 (19–25)	0.117
GGT (U/L)	19 (15–30)	20 (17–32)	0.398
Glycated hemoglobin (%)	5.6 (5.5–5.8)	5.8 (5.6–6.1)	**0.003**
Transient elastography			
CAP (dB/m)	236 (211–247)	304 (283–337)	**< 0.001**
Liver stiffness (kPa)	4.6 (3.5–5.9)	4.9 (3.8–6.0)	0.569

Note: Values are median (IQR) or number of participants and percentages (in brackets). Blood values represent standard clinical parameters: glucose, lipid profile, and glycated hemoglobin (metabolic status), and AST, ALT, and GGT (liver function tests). Bold values indicate statistically significant differences ($p < 0.05$).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; GGT, gamma glutamyltranspeptidase.
[a]Second visit was performed after a median of 5 years from the first visit.
[b]Metabolic syndrome was defined by the presence of 3 or more of the following features: a/waist circumference > 102 cm in men or > 88 cm in women; b/serum triglycerides > 150 mg/dL; c/high-density lipoprotein (HDL) cholesterol levels < 40 mg/dL in men or < 50 mg/dL in women; d/systolic blood pressure > 130 mmHg or diastolic blood pressure > 85 mmHg; and e/fasting plasma glucose > 110 mg/dL.

Specifically, the presence of steatosis, estimated by CAP, using a cutoff similar to that applied in the current study, showed AUROCs of 0.76 and 0.87 for histologically confirmed steatosis in two cohorts of patients with MASLD [18, 19]. Moreover, the effect of therapeutic maneuvers that cause a reduction in fat liver content (decrease in body weight either due to bariatric surgery or lifestyle modifications) is associated with a parallel decrease in CAP values [20–22]. In fact, a study evaluating the effect of lifestyle changes on hepatic steatosis in a group of patients with MASLD showed a parallel reduction in CAP values compared to values of MRI-PDFF [23]. Therefore, although MRI-PDFF and liver biopsy remain as the gold standard for the assessment of steatosis, it is currently accepted that CAP is an accurate, non-invasive method for assessing changes in liver fat content [23, 24].

In the current study, the threshold of changes in CAP to define resolution of hepatic steatosis was a decrease of 10% in the second visit compared to the first visit; likewise, the threshold to define development of hepatic steatosis was an increase of 10%. The selection of this percent change was based on findings of our preliminary study specifically performed for the purpose of assessing variability of CAP values in two determinations on different days. This percent change is similar to that reported in other studies assessing CAP variability [15, 25, 26]. It should be emphasized that in our cross-sectional study in volunteers, CAP variability was lower in participants with higher CAP values, a finding consistent with that of a previous study in a cohort of patients with MASLD [15]. However, the possibility of greater variability among participants with high CAP values cannot be entirely excluded. Moreover, in the definition it was also required that values of CAP in the second TE measurement were either below or above 275 dB/m for the diagnosis of resolution or development of steatosis, respectively, a cutoff widely accepted for diagnosis of steatosis [9]. The use of these

TABLE 4 | Comparison of differences (delta) between participants with steatosis resolution and development of steatosis.

Δ	Resolution of steatosis ($n = 30$)	Development of steatosis ($n = 31$)	p value
Demographic and clinical			
Weight (kg)	−1.55 (−7.15 to 1.73)	3.00 (−2.15 to 6.5)	**0.019**
Waist circumference (cm)	0 (−3 to 2)	1.8 (−0.9 to 8.9)	0.060
BMI (kg/m^2)	−0.66 (−2.82 to 0.84)	0.64 (−0.65 to 2.60)	**0.015**
Biochemical profile			
Glucose (mg/dL)	−4 (−11 to 3)	−5 (−8 to 3)	0.608
Total cholesterol (mg/dL)	−7 (−40 to 9)	3 (−18 to 14)	0.157
LDL-cholesterol (mg/dL)	−6 (−23 to 5.3)	5 (−19 to 12)	0.173
HDL-cholesterol (mg/dL)	4 (−7 to 8)	0 (−6 to 7)	0.734
Triglycerides (mg/dL)	−6 (−49 to 18)	10 (−33 to 30)	0.145
AST (U/L)	−3 (−5 to 1)	1 (−1 to 4)	**0.002**
ALT (U/L)	−5 (−8 to 0)	1 (−2 to 6)	**0.002**
GGT (U/L)	−4 (−11 to 0)	1 (−3 to 5)	**0.018**
Glycated hemoglobin (%)	−0.1 (−0.4 to 0.3)	0.2 (0–0.5)	**0.026**
Transient elastography			
CAP (dB/m)	−98 (−120 to −62)	73 (48–97)	**< 0.001**
Liver stiffness (kPa)	−0.1 (−1.6 to 0.6)	0.1 (−0.8 to 0.9)	0.149

Note: Values are median (IQR). Blood values represent standard clinical parameters: glucose, lipid profile, and glycated hemoglobin (metabolic status), and AST, ALT, and GGT (liver function tests). Bold values indicate statistically significant differences ($p < 0.05$).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; GGT, gamma glutamyltranspeptidase.

definitions allowed us the identification of two groups of participants with marked changes in their CAP values between the two studies (Figure 2). In fact, in participants with resolution of hepatic steatosis, the median reduction of CAP was 98 dB/m with a final value of only 237 dB/m. These changes are of a magnitude similar to that reported in obese participants treated with bariatric surgery, intense lifestyle intervention or GLP-1 agonists, three methods known to have a marked effect in reducing fatty liver content [27–29]. On the other hand, in participants with steatosis development, the median increase in CAP was 73 dB/m with a median final value of 304 dB/m. The findings of our study are in keeping with those recently reported in a cohort of 1042 participants from the general population and at-risk population of SLD, as defined by CAP ≥ 275 dB/m, that were studied on two occasions 2 years apart [30]. Interestingly, this study found very similar percentages of SLD resolution and development (33% and 25%, respectively) compared to those found in the current study (34% and 29%, respectively). Although both studies have differences with respect to the populations studied and etiologies of SLD, the results support the concept that steatosis is a very dynamic process and changes over time are very common.

The main factors associated with the resolution/development of steatosis were changes in body weight, BMI, and waist circumference. Interestingly, resolution of hepatic steatosis occurred despite the risk factors of metabolic liver disease did not disappear completely. However, it is likely that not only the presence of risk factors but also their intensity is important for the deposition of fat in the liver. Hepatic steatosis is frequently associated with liver inflammation and development of liver fibrosis in a subset of individuals [31, 32]. In our cohort, resolution of steatosis was associated with a reduction in transaminases and GGT levels, whereas development of steatosis was associated with the opposite changes; however, median levels of transaminases and GGT in the whole series were within normal limits. Overall, no changes were observed in LSM.

An intriguing aspect of the study was the resolution of hepatic steatosis in one-third of the participants with baseline steatosis, despite the absence of any formal intervention. Although CAP and LSM results were shared with participants, no therapeutic action was taken [11]. However, TE itself may have triggered lifestyle changes, as previously observed [33, 34]. Alternatively, unrecognized changes in behavior could also explain the improvement in liver fat content.

The strengths of the current study are that it was performed in participants from the general population, thus avoiding a possible bias that could have resulted from the evaluation of participants seen in the hospital setting. Moreover, there was a long period of time between the first and second visits, so that spontaneous variations within the natural history of steatosis could be captured. Therefore, the study likely reflects the natural history of SLD related to MASLD in participants from the general population. The weaknesses of the study are mainly related to the relatively low sample size of the cohort, which limits the interpretation of subgroup analyses, and to the fact that the study was performed in only one country with the majority of participants being of Caucasian origin, so that it is not known whether the

findings observed also apply to different ethnic groups. Moreover, the study has the intrinsic bias of the identification of participants through the registry of people attending a primary health care center; therefore, people of deprived groups (i.e., illegal immigrants) were likely not included. Finally, the participants had a relatively high median age, probably related to the method used for identification. Further studies in larger cohorts, including participants from different ethnic and socioeconomic groups, and encompassing all age ranges, should be conducted.

In conclusion, the results of the current study show that within a 5-year period there are marked changes in fat liver content in participants from the general population, with one third of participants with SLD showing resolution of steatosis and one third of participants with normal liver developing SLD during the same period. These variations were mainly related to changes in body weight and were accompanied by corresponding changes in liver tests, specifically transaminases and GGT. These results are of interest to the natural history of SLD related to MASLD.

Author Contributions

Conceptualization: N.F., I.G., P.G., M.C. Data curation: M.C., M.P.-G., M.C., R.N., M.S.-R., M.P., G.S., Q.H. Formal analysis: M.C., A.J., P.G., I. G., N.F. Supervision: N.F., I.G., P.G., A.J., R.H., A.S., E.P.

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Conflicts of Interest

P.G. has received research funding from Gilead and Grifols. P.G. has consulted or attended advisory boards for Gilead, RallyBio, SeaBeLife, Merck, Sharp and Dohme, Ocelot Bio, Behring, Roche Diagnostics International, Boehringer Ingelheim, and Astra-Zeneca, and received speaking fees from Pfizer. A.S. is co-funded by a Río Hortega grant and the European Union (expedient CM23/00133), Instituto de Salud Carlos III, Acción Estratégica en Salud, December 2023 Call.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy and ethical restrictions. Data are available from the corresponding author upon reasonable request and with permission of the Hospital Clínic Ethics Committee.

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Supporting Information

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