Hepatic Fat in Participants With and Without Incident Diabetes in the Diabetes Prevention Program Outcome Study

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Abbreviations: BMI, body mass index; BP, blood pressure; CAC, coronary calcium scoring; CRP, high-sensitivity C-reactive protein; CT, computed tomography; DMGV, dimethylguanidinovaleric acid; DPP, Diabetes Prevention Program; DPPOS, Diabetes Prevention Program Outcome Study; FG, fasting plasma glucose; FI, fasting insulin; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HU, Hounsfield units; IGT, impaired glucose tolerance; LA, liver attenuation; LDL-C, low-density lipoprotein cholesterol; MESA, Multiethnic Ethnic Study of Atherosclerosis; NAFLD, nonalcoholic fatty liver disease; ROI, region of interest; tPA, tissue plasminogen activator.

Received: 20 October 2020; Editorial Decision: 8 March 2021; First Published Online: 11 March 2021; Corrected and Typeset: 7 September 2021.

Abstract

Context: There is little information about fatty liver in prediabetes as it transitions to early diabetes.

Objective: This study is aimed at evaluating the prevalence and determinants of fatty liver in the Diabetes Prevention Program (DPP).
Methods: We measured liver fat as liver attenuation (LA) in Hounsfield units (HU) in 1876 participants at ~14 years following randomization into the DPP, which tested the effects of lifestyle or metformin interventions versus standard care to prevent diabetes. LA was compared among intervention groups and in those with versus without diabetes, and associations with baseline and follow-up measurements of anthropometric and metabolic covariates were assessed.

Results: There were no differences in liver fat between treatment groups at 14 years of follow-up. Participants with diabetes had lower LA (mean ± SD: 46 ± 16 vs 51 ± 14 HU; \( P < 0.001 \)) and a greater prevalence of fatty liver (LA < 40 HU) (34% vs 17%; \( P < 0.001 \)). Severity of metabolic abnormalities at the time of LA evaluation was associated with lower LA categories in a graded manner and more strongly in those with diabetes. Averaged annual fasting insulin (an index of insulin resistance [OR, 95% CI 1.76, 1.41-2.20]) waist circumference (1.63, 1.17-2.26), and triglyceride (1.42, 1.13-1.78), but not glucose, were independently associated with LA < 40 HU prevalence.

Conclusion: Fatty liver is common in the early phases of diabetes development. The association of LA with insulin resistance, waist circumference, and triglyceride levels emphasizes the importance of these markers for hepatic steatosis in this population and that assessment of hepatic fat in early diabetes development is warranted.

Key words: Lipid metabolism, weight regulation and obesity, prediction and prevention of type 2 diabetes, imaging, hepatic fat, diabetes development, lifestyle, metformin

Fatty liver is common in type 2 diabetes and is associated with increased morbidity and mortality (1). The accumulation of liver fat in diabetes is thought to result from increased hepatic fatty acid availability and deposition as triglyceride contributing to the development of hepatic insulin resistance and increased hepatic glucose and triglyceride output (2). These metabolic abnormalities are part of the pathophysiology leading to diabetes, and fatty liver is known to both predate (3) and predict (4) the development of diabetes. Since prediabetes is the precursor to diabetes, such individuals should be susceptible to fatty liver. However, there is little information about the prevalence of fatty liver in categorically defined prediabetes and early diabetes. It is known that prediabetes is a common finding in subjects with nonalcoholic fatty liver disease (NAFLD) and the prevalence of fatty liver increases in relation to the glycated hemoglobin A1c (HbA1c) level in nondiabetic subjects (3), suggesting that dysglycemia is a risk factor for fatty liver. Nevertheless, there have been no systematic studies of liver fat and its determinants in populations with defined prediabetes nor what the impact of diabetes development is on liver fat in these individuals.

The Diabetes Prevention Program Outcome Study (DPPOS) is the long-term follow-up study of the Diabetes Prevention Program (DPP) a placebo-controlled randomized clinical trial that demonstrated in overweight subjects with impaired glucose tolerance (IGT) that intensive lifestyle or metformin interventions reduced diabetes development compared to placebo plus standard care over a 2.8-year period by 58% and 31%, respectively (5). These interventions also had differing effects on body weight, insulin sensitivity, and circulating lipids (5). Treatment group differences in diabetes incidence persisted following this initial intervention period, with 27% and 18% reductions in diabetes incidence for lifestyle and metformin, respectively, at year 11 of DPPOS, approximately 15 years after randomization (6). DPPOS is evaluating the long-term effects of these interventions on diabetes development and its complications. To this end, computed tomographic (CT) studies were performed at year 10 of DPPOS, approximately 14 years after randomization for coronary calcium scoring (CAC) (7) and included axial slices through the liver, providing an opportunity to assess the characteristics, metabolic features, and determinants of liver fat in those who developed diabetes versus those who did not in a secondary analysis.

Methods

DPP and DPPOS Design, Randomization, and Masking

Selection criteria for the DPP (ClinicalTrials.gov registration no. NCT00004992) included: age ≥ 25 years, body mass index (BMI) ≥ 24 kg/m² (≥22 kg/m² in Asian Americans), fasting plasma glucose (FG) levels between 5.3 and 6.9 mmol/L (<6.9 mmol/L in American Indians), and IGT (2-hour post-load glucose of 7.8-11.0 mmol/L). Written informed consent was obtained from all participants before screening, consistent with the Declaration of Helsinki and the guidelines of each center’s institutional
review board. In total, 3234 participants were originally randomly assigned to 1 of 3 interventions: metformin 850 mg or placebo twice daily with double blinding, or an intensive program of lifestyle modification. The goals of intensive lifestyle change were to achieve and maintain weight reduction of at least 7% through consumption of a low-calorie, low-fat diet and to engage in at least 150 minutes/week of physical activity. The placebo group was managed according to standard healthcare recommendations only. Diabetes was diagnosed on the basis of an annual oral glucose tolerance test or a semiannual fasting plasma glucose test according to American Diabetes Association criteria (8) and required confirmation by a second test, usually within 6 weeks. Once diabetes was diagnosed or an HbA1c of ≥53mmol/mol was reached in the metformin group, study drug was discontinued and diabetes management, including treatment with metformin or other medicines was transferred to the participant’s health care provider. At DPP-end, placebo and metformin groups were unmasked to their treatment assignment, and all participants were offered intensive lifestyle intervention in a group format during a 1-year bridge period. All surviving consented DPP participants (n = 3149), regardless of diabetes status, were invited to participate in the DPPOS and 2776 (88%) joined (6). In addition to maintenance group lifestyle sessions offered to all participants, the original lifestyle group was offered supplementary group programs reinforcing behavioral self-management activities twice per year. During DPPOS, metformin, now unmasked, continued to be provided to participants randomized to metformin who remained eligible.

**Clinical and Metabolic Variables**

Standardized questionnaires were used to obtain demographic and clinical data. BP, height, and weight were measured using standardized techniques. HbA1c, FG, fasting insulin (FI, as a measure of insulin resistance), lipid profile, high-sensitivity C-reactive protein (CRP), adiponectin, and plasma tissue plasminogen activator (tPA) (as a surrogate for plasminogen activator inhibitor 1 [PAI-1] measurements) were performed at the Central Biochemistry Laboratory (Northwest Lipid Research Laboratories, University of Washington, Seattle) as previously reported (9, 10). These assessments were performed at baseline and annually thereafter except for CRP, adiponectin, and tPA, which were measured at baseline and DPP year 1; tPA and CRP were also measured at DPPOS year 1 and CRP additionally at DPPOS year 5. Dimethylguanidinovaleric acid (DMGV), a recently identified metabolite biomarker of CT-defined NAFLD, was measured at baseline only, by liquid chromatography-accurate-mass tandem mass spectrometry (11) in 1276 participants and values were normalized by transformation to have a mean of 0 and an SD of 1. CAC scoring, prevalence of dyslipidemia (annually) and microangiopathy (at year 11) were assessed by previously reported methods (6, 7).

**Hepatic fat measurements**

(i) Image acquisition

Each eligible participant underwent 2 consecutive nonenhanced cardiac CT scans during a single session. We studied 1876 of the original 2776 DPPOS participants (68%), comprising active DPPOS participants with no condition excluding them from CT scanning, not drinking >7 alcoholic drinks/week in women or >14 drinks/week in men nor having known hepatitis other than NAFLD, not taking steroids or amiodarone, and who volunteered for the study. Participants were scanned by multi–detector row CT scanners by certified technologists at each clinical site using electrocardiogram-triggered scan acquisition at 50% of the R-R interval using a 2.5-mm slice thickness from the carina to below the apex of the heart and containing images of the liver and spleen. The images were transferred to the central reading center (Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, California). Two experienced readers independently read all CT scans in a manner blinded to patient characteristics and treatment assignment.

(ii) Liver fat measurements

Both scans for each participant were examined and the one with the largest liver scan span was selected for measurement of liver fat (12). Liver attenuation (LA) was measured as Hounsfield unit (HU) values using regions of interest (ROI) > 100 mm² in area. Two ROIs were placed in the right liver lobe anteroposteriorly. ROIs with larger areas were used whenever possible to include a greater area of the liver while taking care to exclude regions of nonuniform parenchymal attenuation, including hepatic vessels. Seventy individuals had inadequate visualization of the liver, leaving a final total of 1876 participants for analysis of hepatic fat. Since 189 scans did not contain images of the spleen, hepatic fat was expressed as liver attenuation only rather than liver/spleen attenuation ratio. Compared with the 900 participants who did not have a scan, at the DPP baseline examination these 1876 participants had slightly higher minority race/ethnicity representation (48% vs 40% non-white), were younger (50.2 vs 52.9 years), had similar BMI (33.7 vs 34.0 kg/m²), and lower systolic blood pressure (BP) (122.7 vs 125.6 mm Hg), but the proportion having hepatic fat measurements did not differ between treatment groups. Data were assumed to be missing...
at random. Figure 1 shows the CONSORT [Consolidated Standards of Reporting Trials] flow diagram.

Statistical Methods
The 2 primary liver fat outcome measures were mean LA and LA < 40 prevalence. Hepatic fat was analyzed as a continuous variable (LA in HU), where lower LA indicates a greater amount of hepatic fat (13) and in categories of LA (2-category outcome: LA < 40, ≥40, and 3-category outcome: LA < 40, 40–50, >50), where LA < 40 is taken to indicate a fatty liver (≥30% fat) (12, 13). Although liver fat prevalence categories are typically presented using the 2-category outcome, namely LA < 40 and ≥40, we also explored whether a 3-category outcome was of value in this population (13).

Differences among subgroups were assessed using ANOVA and Kruskal-Wallis nonparametric tests for continuous and chi-square tests for categorical measures. Trend tests across the 3-category LA outcome for continuous covariates were assessed with a rank-based test of monotonicity (ie, test of Spearman correlation = 0), and for binomial covariates the 2-sided Cochran-Armitage test of proportions was used. Model-based association of covariates with outcomes were assessed using linear, logistic, and/or multinomial models, according to the nature of the outcome. The only exception was for CAC measured as log(CAC+1), where P values were calculated from a tobit model because of the large number of participants with a CAC measurement of zero (7). Separate models tested for effects of baseline covariates and for baseline-adjusted mean annual follow-up measures of covariates. All models were developed without diabetes status in the model except where stated. Measures of association were expressed as differences in mean LA in linear models, odds ratios for LA < 40 in logistic models, and odds ratios for LA < 40 and LA 40 to 50 in the multinomial models using LA > 50 as the referent. Increased hepatic fat is indicated by negative changes in mean LA and odds ratios > 1 for LA categories.

Results
Characteristics of the Cohort
Table 1 shows the characteristics of the cohort of 1876 participants in this study at DPP baseline and at the time of the scan in year 10 of DPPOS (average 13.7 years after
randomization) by intervention group. There were significant differences from placebo in the metformin group for FG, in the lifestyle group for triglyceride, adiponectin, and diabetes incidence, and for tPA values and diabetes duration in both active intervention groups. Diabetes had developed in 52% (n = 319) of the lifestyle, 54% (n = 333) of the metformin, and 60% (n = 382) of the placebo groups (total n = 1034) at the time of the scan. Despite these group differences, there were no differences in mean LA or prevalence of LA < 40 by intervention groups. Therefore, the data from the treatment groups were pooled in all analyses and stratified by diabetes status. Treatment effects did not differ in demographic subgroups but there was a significant diabetes × treatment group interaction (P < 0.01) for both mean LA and LA < 40. Pairwise comparisons demonstrated that within the nondiabetes subgroup, percent LA < 40 was nominally greater and mean LA was lower with metformin versus placebo and lifestyle treatments. The opposite was true in the diabetes subgroup, where percent LA < 40 was less and mean LA greater with metformin treatment versus

| Table 1. Characteristics (mean ± SEM or mean [95%CI]) of the cohort at DPP baseline and at the time of the scan (except where noted) |
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| **DPP baseline (mean ± SEM)** | **Mean [95% CI] during scan year** |
| **All** | **Lifestyle** | **Metformin** | **Placebo** |
| N | 1876 | 615 | 620 | 641 |
| Age at baseline and scan (y) | 50.2 ± 0.2 | 64.1 [63.4, 64.9] | 64.1 [63.3, 64.9] | 63.4 [62.7, 64.2] |
| Race | | | | |
| White | 972 (51.8%) | 309 (50.2%) | 334 (53.9%) | 329 (51.3%) |
| Black | 399 (21.3%) | 131 (21.3%) | 134 (21.6%) | 134 (20.9%) |
| Hispanic | 309 (16.5%) | 100 (16.3%) | 101 (16.3%) | 108 (16.8%) |
| Asian | 87 (4.6%) | 37 (6.0%) | 20 (3.2%) | 30 (4.7%) |
| American Indian | 109 (5.8%) | 38 (6.2%) | 31 (5.0%) | 40 (6.2%) |
| Sex | | | | |
| Female | 1303 (69.5%) | 426 (69.3%) | 426 (68.7%) | 451 (70.4%) |
| Male | 573 (30.5%) | 189 (30.7%) | 194 (31.3%) | 190 (29.6%) |
| Height (cm) | 170.5 ± 0.4 | 169.7 ± 0.4 | 169.8 ± 0.4 | 169.7 ± 0.4 |
| Weight (kg) | 84.1 ± 0.3 | 84.4 ± 0.3 | 84.5 ± 0.3 | 84.4 ± 0.3 |
| BMI (kg/m²) | 33.7 ± 0.1 | 33.6 ± 0.1 | 33.6 ± 0.1 | 33.6 ± 0.1 |
| Waist circumference (cm) | 104.4 ± 0.3 | 104.4 ± 0.3 | 104.4 ± 0.3 | 104.4 ± 0.3 |
| Fasting glucose (mmol/L) | 5.9 ± 0.0 | 6.7 [6.5, 6.8] | 6.5 [6.3, 6.6] | 6.9 [6.7, 7.0] |
| 2-hour glucose (mmol/L) | 9.1 ± 0.0 | 8.3 [8.0, 8.5] | 8.2 [8.0, 8.5] | 8.2 [7.9, 8.5] |
| HbA1c (mmol/mol) | 41.3 ± 0.1 | 43.7 [42.7, 44.8] | 43.1 [42.1, 44.1] | 44.4 [43.4, 45.5] |
| Fasting insulin (pmol/L) | 185.1 ± 0.1 | 238.2 [219.7, 256.6] | 254.5 [236.2, 272.7] | 262.8 [244.8, 280.8] |
| Incident diabetes | | 319 (52%) | 333 (54%) | 382 (60%) |
| Diabetes duration (y) | | 7.4 [7.0, 7.8] | 8.5 [8.1, 8.9] | 9.1 [8.7, 9.5] |
| Metabolic syndrome | | 263 (43%) | 266 (43%) | 316 (49%) |
| Systolic BP (mm/Hg) | 122.7 ± 0.3 | 121.0 [119.8, 122.2] | 121.4 [120.2, 122.6] | 121.0 [119.8, 122.1] |
| Diastolic BP (mm/Hg) | 78.1 ± 0.2 | 71.0 [70.2, 71.7] | 71.3 [70.6, 72.1] | 71.0 [70.2, 71.7] |
| Antihypertensive use | | 4% | 346 (58%) | 337 (59%) | 373 (59%) |
| Triglyceride (mmol/L) | 1.8 ± 0.0 | 1.4 [1.4, 1.5] | 1.4 [1.4, 1.5] | 1.4 [1.4, 1.5] |
| HDL-C (mmol/L) | 1.2 ± 0.0 | 1.4 [1.4, 1.4] | 1.4 [1.4, 1.4] | 1.4 [1.4, 1.4] |
| LDL-C (mmol/L) | 3.2 ± 0.0 | 2.6 [2.6, 2.7] | 2.6 [2.5, 2.6] | 2.6 [2.5, 2.6] |
| Statin use | | 4% | 329 (55%) | 357 (59%) | 373 (59%) |
| CRP (nmol/L) | 0.6 ± 0.0 | 0.5 [0.4, 0.5] | 0.4 [0.4, 0.5] | 0.5 [0.4, 0.5] |
| Adiponectin (ug/mL) | 7.9 ± 0.1 | 8.8 [8.5, 9.1] | 8.2 [7.9, 8.5] | 7.9 [7.6, 8.2] |
| tPA (ng/mL) | 10.0 ± 0.1 | 9.0 [8.7, 9.3] | 8.0 [7.7, 8.3] | 9.6 [9.3, 9.9] |
| Baseline ALT (U/L) | 20.3 ± 0.3 | N/A | N/A | N/A |
| Baseline AST (U/L) | 20.5 ± 0.2 | N/A | N/A | N/A |
| LA < 40 HU | N/A | 143 (23%) | 154 (25%) | 163 (25%) |
| Liver attenuation (HU) | N/A | 48.6 [47.4, 49.8] | 48.6 [47.4, 49.8] | 47.6 [46.4, 48.8] |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CRP, high-sensitivity C-reactive protein; DPP, Diabetes Prevention Program; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HU, Hounsfield units; LA, liver attenuation; LDL-C, low-density lipoprotein cholesterol; tPA, tissue plasminogen activator.  

1P < 0.05 for baseline-treatment group comparison.  

2P < 0.05 for difference from placebo for lifestyle and/or metformin groups at follow-up.  

3P < 0.05 for comparison of follow-up lifestyle and metformin groups.
the other 2 groups. The only pairwise comparisons that reached significance \( P < 0.05 \) were for LA < 40 within the nondiabetes group for metformin versus placebo.

**Distribution of Mean LA and LA < 40 by Demographic Factors and Nondiabetes/Diabetes Status**

Figures 2A and 2B present mean LA and prevalence of LA < 40 for the entire cohort by intervention groups, demographic factors, and diabetes status. Overall mean LA was 48.2 HU and LA < 40 prevalence was 25%. Those with diabetes at the time of scanning had lower mean LA values than those without diabetes (46 ± 16 vs 51 ± 14 HU; \( P < 0.001 \)), and the prevalence of LA < 40 was about twice that in those without diabetes overall (31% vs 17%; \( P < 0.001 \)) and in all race/ethnic groups except for African Americans, where there was no difference between those with versus without diabetes. Mean LA was higher in African Americans than non-Hispanic Whites and Hispanics (54.7 vs 47.4 HU; \( P < 0.001 \) for both) and LA < 40 prevalence lower (9.8% vs 25.8%; \( P < 0.001 \) for both), whereas the opposite was true for American Indians vs non-Hispanic Whites overall (mean LA: 40.3 vs 47.4 HU and LA < 40: 44.0% vs 25.8%; \( P < 0.001 \) for both) as well as in those with or without diabetes. There was also an inverse age trend toward lower mean LA (44.6, 48.2, 53.5 HU in those <60, 60 to 69, and >70 years of age; \( P < 0.001 \)) and greater LA < 40 prevalence (33.7%, 24.7%, 11.5%; \( P < 0.001 \)). There was no heterogeneity in these associations by diabetes status. Sex was not associated with liver fat (mean LA: 47.9 HU in males vs 48.4 HU in females) nor the proportion with LA < 40 (23% in males vs 25% in females).

**Figure 3** presents the LA frequency distribution in the groups with and without diabetes. Although there is considerable overlap, the distribution of LA values in the group with diabetes was different from those without diabetes (\( P < 0.001 \)) and is shifted toward lower attenuation, with medians of 48.6 and 54.1 HU in the groups with and without diabetes respectively.

**Cross-Sectional Associations of Metabolic and Clinical Factors With LA Categories**

We next evaluated whether LA expressed as a 3-category outcome was related to standard metabolic and clinical abnormalities at the time of the scan and how these relationships differed by diabetes status (Table 2). The prevalence of LA < 40 HU in those with diabetes compared to those without was higher (30.5% vs 17.3%) and of LA > 50 was lower (47% vs 62.1%). Comparing those with and without diabetes, all metabolic and clinical variables were higher in the group with diabetes except high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) values, which were lower. There were graded differences in glycemic measures, FI, anthropometric measures, triglyceride, and HDL-C values and also prevalence of metabolic syndrome by LA categories within each of the 2 subgroups, with significant interactions for glycemia measures, FI, and LDL-C between diabetes status subgroups and LA categories. Among participants with diabetes, mean LA trended higher with increased

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**Figure 2.** Mean (black dot) LA in HU and 95% CI (shaded bar) (Panel A) and prevalence of LA < 40 HU and 95% CI (Panel B) by intervention groups, demographic factors, and diabetes status.
diabetes duration and there was a significant though weak positive correlation between diabetes duration and mean LA ($r^2 = 1\% ; P < 0.01$). This was not accounted for by age or influenced by treatment group in separate analyses (data not shown). There were no differences in prevalence of hypertension, microangiopathy, or CAC scores by LA categories.

Baseline Predictors of Liver Attenuation

Given the associations between anthropometric and metabolic factors and mean LA we then examined whether LA was predicted by these factors as well as several other biomarkers for increased liver fat that were available in DPP at entry into the study by analyzing their associations adjusted for demographics (age, sex, race), and treatment group with LA values (Fig. 4A; Model 1). All except HbA1c and FG were associated with mean LA in an inverse manner signifying greater liver attenuation per 1 SD of the covariate, except for adiponectin and HDL-C which were directly related. After including all these variables in a single model (Fig. 4A; Model 2), FI, DMGV, and tPA (inversely) and adiponectin (directly) remained independently associated while waist circumference did not. Individual associations with prevalence of LA < 40 were similar to those for mean LA (Fig. 4B; Model 1), with FI, tPA, adiponectin, and FG remaining associated after adjustment for other baseline covariates (Fig. 4B; Model 1). The direction of the effects was concordant for the 2 outcomes.

Predictors of Liver Attenuation During Follow-Up

Considered individually in analyses adjusting for baseline value, demographics, and treatment group, all averaged annual variables were related to mean LA (Fig. 5A; Model 1) and LA < 40 prevalence (Fig. 5B; Model 1) with the exception of adiponectin for the LA outcome. When all baseline and averaged annual terms plus adjustment for demographics and intervention group were combined (Figs 5A and 5B; Model 2) only waist, triglyceride, and FI remained significantly associated with the hepatic fat measures for both outcomes. Addition of diabetes status to these models did not change these associations (Fig. 6).

Diabetes and Liver Attenuation

We then investigated whether these 3 variables, waist, FI, and triglyceride accounted for the difference in LA in those
with versus without diabetes by assessing the effects of these variables on the ratios of mean LA and on the 3-category LA outcome by diabetes status. In addition, because those with diabetes had higher HbA1c values, time-averaged HbA1c was also evaluated. The models tested the added effect of each variable after adjusting for baseline values, demographics, and treatment group (Fig. 7) by comparing the ratio of the geometric means of LA (panel A) and the odds of severe hepatic fat (LA < 40:LA > 50) and moderate hepatic fat (LA 40-50:LA > 50) in those with versus without diabetes (panel B). Being in the diabetes group was associated with increased hepatic fat (ie, decreased mean LA ratio in panel A or increased odds of LA < 40 or LA 40-50 versus > 50 in panel B) for all models except LA 40 to 50 in models 4 and 6. Simultaneous adjustment for waist, FI, HbA1c, and triglycerides did not fully account for

Table 2. Metabolic factors and clinical measures (median [IQR] or N [%]) during the year of the scan

|                  | No Diabetes | Diabetes | P*  |
|------------------|-------------|----------|-----|
|                  | LA < 40     | LA 40-50 | LA > 50 |
| N                | 142         | 173      | 527  |
| LA category prevalence | 17.3%       | 20.6%    | 62.1% |
| Female           | 105 (74%)   | 112 (65%)| 367 (70%) |
| Caucasian        | 79 (56%)    | 102 (59%)| 290 (55%) |
| METABOLIC        |             |          |      |
| Fasting glucose (mmol/L) | 5.8 [5.4, 6.2] | 5.8 [5.5, 6.0] | 5.7 [5.3, 6.0] |
| 2-hour glucose (mmol/L) | 8.4 [7.2, 9.7] | 8.4 [7.0, 9.7] | 7.9 [6.5, 9.1] |
| HbA1c (mmol/mol)  | 38.8 [35.5, 40.2] | 37.7 [34.7, 41.0] | 37.4 [34.4, 39.9] |
| Fasting insulin (pmol/L) | 262 [184, 355] | 198 [144, 264] | 162 [111, 227] |
| Triglycerides (mmol/L) | 1.6 [1.2, 2.0] | 1.4 [1.0, 1.8] | 1.1 [0.8, 1.5] |
| HDL-C (mmol/L)    | 1.3 [1.1, 1.5] | 1.3 [1.1, 1.5] | 1.5 [1.2, 1.7] |
| LDL-C (mmol/L)    | 2.9 [2.3, 3.5] | 2.7 [2.2, 3.2] | 2.7 [2.2, 3.2] |
| BMI (kg/m²)       | 34 [30, 39] | 31 [28, 37] | 30 [26, 34] |
| Waist (cm)        | 109 [102, 117] | 106 [98, 114] | 100 [92, 110] |
| DBP (mmHg)        | 73 [67, 79] | 71 [65, 76] | 70 [63, 76] |
| SBP (mmHg)        | 119 [113, 127] | 117 [110, 128] | 119 [110, 130] |
| Diabetes duration (years) | N/A | N/A | N/A |
| Hypertension or on medication | 78 (55.7%) | 85 (49.7%) | 288 (56.8%) |
| Metabolic syndrome | 56 (39.4%) | 53 (30.6%) | 149 (28.3%) |
| Lipid lowering agents | 35 (25%) | 53 (31%) | 165 (32.5%) |
| Antihyperglycemic agents | 12 (8.6%) | 12 (7.0%) | 20 (3.9%) |
| Retinopathy | 11 (8.0%) | 16 (9.5%) | 45 (8.8%) |
| Nephropathy | 9 (6.3%) | 12 (6.9%) | 52 (9.9%) |
| Neuropathy | 10 (7.4%) | 21 (12.7%) | 51 (10.2%) |
| Any microangiopathy | 26 (18.3%) | 44 (25.4%) | 132 (25.0%) |
| CAC (Agatston score) | 4 [0, 62] | 6 [0, 198] | 7 [0, 152] |
| log(CAC+1) | 1.6 [0, 4.1] | 1.9 [0, 5.3] | 2.1 [0, 5] |

Abbreviations: BMI, body mass index; CAC, coronary calcium scoring; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LA, liver attenuation; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

P value for differences between LA categories within no diabetes/diabetes subgroups.

P value < 0.05 for test of diabetes × LA interaction.

P value < 0.05 for chi-square test of LA category prevalences in the 2 diabetes groups.

P value < 0.05 for differences between no diabetes/diabetes subgroups (collapsed across LA categories).

P value < 0.05 for trend test.
the diabetes-related differences in mean LA or odds of fatty liver (LA < 40 vs > 50), although they were attenuated particularly by the addition of FI to the base model.

**Anthropometric Measures and Liver Attenuation**

Figure 8 shows the association between mean LA and average percent changes from baseline in weight (Panel A) and waist until the time of the scan (Panel B) adjusted for demographic and metabolic factors and by diabetes status. Both waist and weight change were strongly and inversely related to mean LA in participants with or without diabetes.

**Discussion**

In this cohort of DPP/DPPOS participants with prediabetes at entry into the trial, we found that 25% of the population had a fatty liver when assessed 14 years later, at which time 56% had developed diabetes using the cutoff of LA < 40 by CT (11, 12). As a comparison, the prevalence of LA < 40...
in 3357 asymptomatic individuals being screened for colon cancer was 6.2% (14) and in the Multiethnic Ethnic Study of Atherosclerosis (MESA), a population-based study, the prevalence of fatty liver using the LA < 40 cutpoint was 6.7% (15). Compared with these populations who were not specifically selected for the presence of higher BMI and glucose intolerance as we did in DPP, the DPPOS cohort had a considerably higher prevalence of fatty liver. These findings were undoubtedly influenced by those who had developed diabetes at the time of the scan, 31% of whom had LA < 40, compared with 17% of those who had not. The prevalence of fatty liver in those with diabetes in MESA was 24% (15), based on a liver/spleen ratio of <1.0 so our findings are not dissimilar. Although the mean duration of diabetes in the diabetes inception cohort in DPPOS was 7.4 to 9.1 years, this should be viewed in the context of time following biochemical diagnosis assessed semi-annually in this study rather than that in clinically diagnosed diabetes which is usually made years later, indicating that fatty liver is prevalent early in the course of diabetes. The results further demonstrate that even those without diabetes in our study, most of whom had persisting prediabetes, had a

Figure 6. Adjusted models of mean LA differences with 95% CI and odds ratios with 95% CI for LA < 40 compared with LA ≥ 40 regressed on demographic, treatment group, and follow-up-averaged, anthropometric, and metabolic factors as in Fig. 5, but with and without diabetes in the models.

Figure 7. Effects of adding adjustment for baseline and mean follow-up values for triglyceride, waist circumference, F1, and HbA1c (Model 2-5) to model 1 adjusted for age, race, sex, and treatment group, comparing mean LA (Panel A) and prevalence of LA categories (Panel B) in the diabetes vs nondiabetes groups. A final model includes adjustment for all the covariates (Model 6). Effects are expressed as the ratio of the geometric mean and 95% CI of LA (Panel A) between diabetes vs nondiabetes from a linear model with logLA as outcome. The odds ratios (95% CI) between diabetes vs nondiabetes of having LA < 40 and LA 40-50 is compared to LA > 50 (Panel B). The x-axis is reversed in Panel A so that values to the right of the null reference line indicate increasing hepatic fat (consistent with Panel B).
higher prevalence of fatty liver than that reported in the general population.

African Americans in DPPOS had a lower prevalence of fatty liver than non-Hispanic Whites, as noted in the Dallas Heart Study, in which hepatic fat was measured in a large urban population using proton magnetic resonance spectroscopy (16) and which was shown to be in part due to the increased frequency of a genetic polymorphism in African Americans associated with lower hepatic fat (17). It is of interest in this regard that despite having lower hepatic fat measurements as well as a lower prevalence of LA < 40, there were no differences in rates of diabetes development in DPP between African Americans and non-Hispanic Whites or Hispanic participants (6). It was also notable that in our study there were no significant differences in hepatic fat between non-Hispanic White, Hispanic, or Asian American subjects, unlike the results reported in the Dallas Heart Study as well as in MESA (16, 18). This discrepancy may have resulted from the per protocol selection of the DPP cohort for a narrow range of glucose intolerance, more limited BMI range, and a smaller sample size for Asians. Since glucose intolerance is more common among minority race/ethnic groups in the general population, this may contribute to population-based race/ethnicity differences in hepatic fat compared with a cohort primarily selected for obesity and glucose intolerance. Despite this, we found that American Indians had a greater prevalence of fatty liver than did non-Hispanic Whites, an observation that to our knowledge has not previously been reported. Although we observed no differences by sex, the finding of an age trend toward higher LA and a lower prevalence of LA < 40 consistent with lower hepatic fat with aging confirms a previous report (19). It was of interest that despite their greater degree of liver fat, these age and race/ethnicity differences were also present in those with diabetes (data not shown).

We found no overall differences in liver fat measures between lifestyle or metformin interventions and placebo treatment. Although a major focus of the lifestyle intervention was to achieve persistent weight loss (5) and weight reduction has been shown to decrease hepatic fat in small studies (20), at the time of the scan there were no significant weight differences between the 3 intervention groups, probably because of the introduction of group lifestyle to the entire cohort in the DPPOS phase. However, there was a strong linear relationship between mean LA and waist or weight change independent of metabolic variables and treatment group over time, supporting an important role for weight reduction in these overweight individuals with glucose intolerance in reducing hepatic steatosis. The finding that long-term metformin treatment had no overall apparent effect on hepatic fat is consistent with previous reports (21) although the finding of a treatment group by diabetes status interaction for mean LA and LA < 40 raises the possibility that metformin may have different effects on liver fat in those with versus without diabetes.
We showed, as others have, that there was a graded relationship between glycemia, insulin resistance as measured by the FI, BMI, and waist circumference, and triglyceride and HDL-C values all assessed during the year of scanning and the amount of hepatic fat by LA categories (2). Furthermore, for any given LA category, the presence of diabetes was associated with greater cardiometabolic disturbance compared with those without diabetes. The fact that we were not able to find an association between LA category and presence of microangiopathy may reflect its low prevalence and severity in this study, and the lack of association with CAC as an index of subclinical coronary heart disease has been reported by others (22).

Since these cardiometabolic risk factors had been assessed yearly from entry into the study approximately 14 years before the scan and in addition several other biomarkers of hepatic steatosis, namely adiponectin (24), tPA (as a surrogate for PAI-1[25]), CRP (26), and DMGV (11) were also measured at baseline and for adiponectin, tPA, and CRP at year 1 and repeated at DPPOS year 1 for tPA and CRP and year 5 for CRP, it was possible to test these variables for their long-term associations with hepatic fat. The association of baseline FI as a measure of insulin resistance, adiponectin, tPA and DMGV with mean LA independent of level of glycemia and other cardiometabolic risk factors measured approximately 14 years later indicates that these are important markers of future hepatic fat accumulation in subjects with glucose intolerance and that the metabolic milieu favoring hepatic fat accumulation develops early in the course of dysglycemia. When fully adjusted average follow-up values of the measured metabolic variables were assessed, FI remained associated but adiponectin, tPA, and DMGV values were no longer significant, although this may have been due to the limited number of follow-up measurements performed for these analytes. Instead, average triglyceride and waist circumference values measured over time, 2 commonly measured clinical tests that have been associated with increased visceral fat (27), were independently related to LA. The fact that waist circumference was not independently associated with hepatic fat at baseline raises the possibility that changes in body fat closer to the time of the scan are more strongly related to the amount of hepatic fat.

The finding that the degree of insulin resistance, level of triglyceride, and waist size averaged over a lengthy follow-up period were each independently associated with the amount of liver fat in a large, diverse cohort with glucose intolerance suggests that these 3 factors were linked to the relatively high prevalence of fatty liver in this population. The basis for these associations is complex, especially for insulin resistance where there is evidence for both cause and effect relationships in that insulin resistance facilitates hepatic fat deposition, while increased liver fat content leads to hepatic insulin resistance (2). A stronger argument may be made that the association between triglyceride and liver fat reflects the effect of increased liver fat on very-low-density lipoprotein production, leading to an increase in plasma triglyceride concentrations (28). However, this interpretation is also complicated by evidence that several genetic polymorphisms that increase the prevalence of fatty liver are not associated with increased triglyceride levels, possibly because of defects in hepatic triglyceride export (17, 29). It is very likely that time-related weight change is a causative factor for increased liver fat (20).

We also found that although average FG and HbA1c in individual analyses were associated with liver fat, this was no longer true when insulin, waist, and triglyceride were included in multivariable models, indicating that progression of dysglycemia per se was not a major correlate of fatty liver in our study, in contrast to reports of others, perhaps because of the truncated range of values predetermined by eligibility for DPP and the relatively modest degrees of hyperglycemia in our cohort. Furthermore, inclusion of diabetes status in the model did not alter these associations. Also contrary to expectations, diabetes duration was associated with lower hepatic fat, although this effect was small. However, despite these strong associations, these metabolic factors only partly accounted for the greater degree of liver fat in diabetes, pointing to the importance of other factors not assessed here (1).

As noted above, a limitation of the study is the absence of liver fat assessment at baseline, since there may have been differences by treatment assignment at entry. Also, the lack of follow-up adiponectin, tPA, and DMGV measurements prevented an adequate assessment of the importance of changes in these biomarkers over time on liver fat. The strengths of the study include the large, multiethnic, carefully selected cohort, the richness of the dataset, the prospective ascertainment of diabetes, and the randomized treatments.

In conclusion, the DPP/DPPOS data demonstrate that fatty liver was prevalent in a population with prediabetes who had been followed for 14 years, during which time 56% developed diabetes, and that fatty liver was almost twice as common as in those with diabetes versus those with persisting prediabetes. Annually averaged measures of waist circumference, insulin resistance, and triglycerides, but not worsening glycemia over the course of the study were independently associated with fatty liver prevalence and accounted for some but not all of the difference between fatty liver prevalence in those with versus without diabetes. Given the published evidence of the risks for progression of NAFLD to nonalcoholic
steatohepatitis and cirrhosis in diabetes (30-32), and its association with the development of micro- and macrovascular disease (33, 34), these findings raise the importance of early recognition of the presence of NAFLD in those with prediabetes.

Acknowledgments

The Research Group gratefully acknowledges the commitment and dedication of the participants of the DPP and DPPOS. Dr. Gerszten is supported by grant DK081572. Dr. Gerszten is supported by grant DK081572.

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Disclosures: The sponsor of this study was represented on the Steering Committee and played a part in study design, how the study was done, and publication. The funding agency was not represented on the writing group, although all members of the Steering Committee had input into the report’s contents. All authors in the writing group had access to all data. The opinions expressed are those of the investigators and do not necessarily reflect the views of the funding agencies. A complete list of Centers, investigators, and staff can be found in the Appendix. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Kieren Mather received a research grant from Novo IIT and has also medication or supply donations with aggregate value >$10 000 for other research studies from Novo, Sanofi, Merck, and Abbott. The other authors declare no conflict of interest.

Data Availability: In accordance with the NIH Public Access Policy, we continue to provide all manuscripts to PubMed Central including this manuscript. DPP/DPPOS has provided the protocols and lifestyle and medication intervention manuals to the public through its public website (https://www.dppos.org). The DPPOS abides by the NIDDK data sharing policy and implementation guidance as required by the NIH/NIDDK (https://www.niddkrepository.org/studies/dppos/).

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