The Relationship Between Body Fat Distribution and Nonalcoholic Fatty Liver in Adults With Type 1 Diabetes

Erika B. Parente,[1,2,3] Emma H. Dahlström,[1,2,3] Valma Harjutsalo,[1,2,3,4] Jussi Inkeri,[1,5] Stefan Mutter,[1,2,3] Carol Forsblom,[1,2,3] Niina Sandholm,[1,2,3] Daniel Gordin,[1,2,3,6] and Per-Henrik Groop,[1,2,3,7] on behalf of the FinnDiane Study Group

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OBJECTIVE

Obesity, which is associated with nonalcoholic fatty liver (NAFL), has increased among people with type 1 diabetes. Therefore, we explored the associations between body fat distribution and NAFL in this population.

RESEARCH DESIGN AND METHODS

This study included 121 adults with type 1 diabetes from the Finnish Diabetic Nephropathy (FinnDiane) Study for whom NAFL was determined by magnetic resonance imaging. Body composition was assessed by dual-energy X-ray absorptiometry. Genetic data concerning *PNPLA3* rs738409 and *TM6SF2* rs58542926 were available as a directly genotyped polymorphism. Associations between body fat distribution, waist-to-height ratio (WHtR), BMI, and NAFL were explored using logistic regression. A receiver operating characteristic (ROC) curve was used to determine the WHtR and BMI thresholds with the highest sensitivity and specificity to detect NAFL.

RESULTS

Median age was 38.5 (33–43.7) years, duration of diabetes was 21.2 (17.9–28.4) years, 52.1% were women, and the prevalence of NAFL was 11.6%. After adjusting for sex, age, duration of diabetes, and *PNPLA3* rs738409, the volume ($P = 0.03$) and percentage ($P = 0.02$) of visceral adipose tissue were associated with NAFL, whereas gynoid, appendicular, and total adipose tissues were not. The area under the curve between WHtR and NAFL was larger than BMI and NAFL ($P = 0.04$). The WHtR cutoff of 0.5 showed the highest sensitivity (86%) and specificity (55%), whereas the BMI of 26.6 kg/m^2 showed 79% sensitivity and 57% specificity.

CONCLUSIONS

Visceral adipose tissue is associated with NAFL in adults with type 1 diabetes, and WHtR may be considered when screening for NAFL in this population.

Nonalcoholic fatty liver disease (NAFLD) is characterized by excessive accumulation of fat in the liver accompanied by insulin resistance and not related to alcohol consumption >30 g/day for men or >20 g/day for women (1). It covers a disease spectrum from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis, which may progress to fibrosis, cirrhosis, and eventually hepatocellular carcinoma (1–3). NAFLD is typically associated with type 2 diabetes, obesity, and insulin

[1]*Folkhälsan Research Center, Helsinki, Finland*
[2]*Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland*
[3]*Abdominal Center, Nephrology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[4]*National Institute for Health and Welfare, Helsinki, Finland*
[5]*HUS Medical Imaging Center, Radiology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[6]*Joslin Diabetes Center, Harvard Medical School, Boston, MA*
[7]*Department of Diabetes, Central Clinical School, Monash University, Melbourne, Australia*

Corresponding author: Per-Henrik Groop, per-henrik.groop@helsinki.fi

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resistance (1,4–7). However, individuals with type 1 diabetes have become more obese during the last decades (8), and NAFLD has also been described in this population (9–12). The prevalence of NAFLD in type 1 diabetes varies from 4.7 to 50% depending on age, sex, duration of diabetes, BMI, glycemic control, serum triglycerides, and on the method used to measure the liver fat content (9–12). Furthermore, NAFLD has been associated with deleterious consequences such as chronic kidney disease (10) and cardiovascular disease in type 1 diabetes (13). Biomarkers of steatosis have limited clinical utility because they often do not accurately quantify the percentage of intrahepatic fat content assessed histologically; thus, imaging techniques are the preferred noninvasive diagnostic tools for assessing fat accumulation in the liver. Unfortunately, proton magnetic resonance spectroscopy, the most precise imaging method, is of limited availability owing to its high costs. Therefore, a feasible, accessible, and cost-efficient tool to screen individuals at higher risk of NAFLD is warranted.

Beyond obesity and type 2 diabetes, the missense rs738409 C>G single nucleotide polymorphism (SNP) of the *PNPLA3* gene, encoding for the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*), is associated with fat accumulation in the liver (1,14). Although the G-allele carriers of rs738409 do not show increased insulin resistance (15,16), the presence of the G allele has been associated with severe hepatic outcomes such as progressive steatohepatitis, liver fibrosis, and also hepatocarcinoma (17). The variant rs58542926 of the transmembrane 6 superfamily member 2 gene (*TM6SF2)* is also associated with NAFLD independent of the genetic variant rs738409 in *PNPLA3* (14).

A recent meta-analysis stressed the importance of central versus general obesity concerning the risk of all-cause mortality (18). Indeed, visceral adipose tissue has been associated with cardiovascular disease, insulin resistance, and NAFL in people with type 2 diabetes and in the general population (4,19,20). However, the relationship between body fat distribution and NAFL in individuals with type 1 diabetes is unknown. Therefore, in the current study of adults with type 1 diabetes, we investigated whether the compartments of body adipose tissue are associated with NAFL by using logistic regression models adjusted for metabolic and genetic variables. Moreover, because the assessment of body fat distribution requires sophisticated and expensive procedures, such dual-energy X-ray absorptiometry (DXA), we studied the associations between the waist-to-height ratio (WHtR), BMI, and NAFL, seeking to find an easy and accessible tool for the identification of NAFL in this population.

RESEARCH DESIGN AND METHODS

Study Participants

All individuals in this study were participants of the Finnish Diabetic Nephropathy (FinnDiane) Study, which is an ongoing, nationwide, prospective, multicenter (93 centers across Finland) study aiming to identify risk factors for type 1 diabetes complications. Type 1 diabetes was defined as age at onset of diabetes <40 years and permanent insulin treatment initiated within 1 year from the diabetes diagnosis. During the FinnDiane study visit, the participants underwent a thorough clinical examination, collection of blood and urine samples, and they completed several questionnaires. From 2011 to 2017, 131 individuals attending the Helsinki University Hospital study center were recruited and underwent hepatic MRI to evaluate their liver fat content as part of their FinnDiane study visit. Those with self-reported daily alcohol consumption ≥30 g for men and ≥20 g for women were not included in this study, nor were those with NAFL and missing data on alcohol consumption. In the group without NAFL, individuals with missing data on alcohol consumption ($n = 50$) were included because they did not have NAFL. Finally, 121 individuals were included in the current analysis of NAFL as the outcome. Of those, 95 individuals had been genotyped for the *PNPLA3* SNP rs738409 and the *TM6SF2* SNP rs58542926, and 84 individuals had data on body composition available assessed by DXA as part of the FinnDiane Study. The study protocol followed the principles of the Declaration of Helsinki as revised in 2000 and was approved by the Helsinki and Uusimaa Hospital District Ethical Committee (Helsinki, Finland). Written informed consent was obtained from each FinnDiane participant before participation.

Liver Fat Assessment

Liver fat content was assessed by MRI with a 3.0-T scanner (Achieva; Philips, Best, the Netherlands) at the Helsinki University Hospital Medical Imaging Center. An abdominal radiologist (J.I.), blinded to all clinical data, evaluated all hepatic MRI examinations. We obtained axial images of the liver using gradient-echo T1-weighted, dual-echo, in-phase (IP) and opposed-phase (OP) sequences. Then, three regions of interest (ROI), with 2.00 cm^2 each, were drawn at the same location of the liver in both IP and OP images, avoiding hepatic vessels on the IMPAX picture archiving and communication system (Agfa-Gevaert, Mortsel, Belgium). Finally, the mean value of the three signal intensities was used (14,21,22). The hepatic fat fraction was calculated from the equation as follows: dual-echo fat fraction (%) = $[(IP - OP)/(2 \times IP)] \times 100$ (22). NAFL was defined based on a hepatic fat fraction of ≥6% (11,14).

Diabetic Kidney Disease Status

The glomerular filtration rate was estimated (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration formula. Individuals with an eGFR <15 mL/min/1.73 m^2, as well as those on dialysis or with kidney transplantation, were not included in this study.

Body Composition and Anthropometric Measures

Body composition was assessed by DXA (Lunar version 16; GE Healthcare, Wauwatosa, WI) according to the manufacturer's instructions, and visceral fat was measured by CoreScan (23). The percentages of adipose tissues were related to total body weight. The term appendicular refers to both legs and arms, central body fat refers to android and visceral adipose tissues, whereas peripheral body fat refers to gynoid and appendicular adipose tissues. BMI was calculated by total body weight in kilograms divided by the square of height in meters. A stretch-resistant tape measure was used to measure waist circumference at the horizontal plane midway of the superior iliac crest and the lower margin of the last rib. Hip circumference

was measured around the widest part of the great trochanters. The waist-to-hip ratio was calculated by dividing the waist circumference by the hip circumference. The WHtR was calculated by dividing the waist circumference by the height. Central obesity was defined by a WHtR $\geq$0.5.

Insulin Sensitivity and Inflammation

Insulin sensitivity was evaluated using an equation to estimate the estimated glucose disposal rate (eGDR) (24) modified for use with HbA_{1c} instead of HbA_1 (25), and serum hs-CRP was used as a surrogate marker of inflammatory status.

Genotyping and Genetic Variants

Based on the known association between NAFL and the SNPs rs738409 and rs58542926 (1,14), we retrieved the genotypes from available genome-wide association study data on all FinnDiane participants. The quality control and genotyping were performed as previously described (26). The SNPs rs738409 and rs58542926 were directly genotyped on the genotyping platform, with no missing data for 95 of the 121 study participants. Genotypes for the *PNPLA3* rs738409 were analyzed using an additive model with alleles coded as 0 (CC) and 1 (GC), and 2 (GG), unless otherwise stated. Owing to the lower frequency of the *TM6SF2* rs58542926, it was not included in the regression models.

Statistical Analyses

Descriptive data are presented as mean ± SD for continuous parametric variables, median (interquartile range) for continuous nonparametric variables, and percentage for categorical variables. For comparison between groups, the independent samples *t* test, Mann Whitney *U* test, and χ^2 test or the Fisher exact test (when the cells had an expected number $<$5) were applied, respectively. We used binary logistic regression analysis to explore the associations between the compartments of body adipose tissue, WHtR, BMI, and NAFL as an outcome, adjusted for potential confounders. BMI and WHtR were analyzed as a continuous variable, and WHtR was scaled by a factor of 10. We limited the number of covariates in each model due to the small number of individuals presenting the outcome. Model 1 was unadjusted. Model 2 was adjusted for unmodifiable risk factors such as age, sex, and duration of diabetes. Model 3 was adjusted for unmodifiable risk factors plus HbA_{1c}. Model 4 was adjusted for unmodifiable risk factors plus triglycerides, and model 5 was adjusted for unmodifiable risk factors plus the rs738409 (*PNPLA3*) G allele count. A receiver operating characteristic (ROC) curve was used to graphically show the associations between WHtR, BMI, and NAFL as well as to evaluate the sensitivity and specificity of different thresholds of each anthropometric measure. *P* values for the differences in area under the curve (AUC) were calculated by a permutation analysis with 10,000 permutations in R software using the pRoc package (27). A two-tailed *P* value $<$0.05 was considered statistically significant. All data were analyzed using IBM SPSS Statistics for Windows 25.0 software (IBM Corp, Armonk, NY), unless otherwise stated. Genotype frequencies were tested for consistency with Hardy-Weinberg equilibrium in controls before the analysis, using the Fisher exact test in plink v1.09.

RESULTS

In the total of 121 individuals, the median age was 38.5 (32.3–43.7) years, duration of diabetes was 21.2 (17.9–28.4) years, 52.1% were women, 50.4% presented with central obesity (WHtR $\geq$0.5), and the prevalence of NAFL was 11.6% ($n = 14$).

Genetic data for the *PNPLA3* rs738409 and the *TM6SF2* rs58542926 SNPs were available for 78.5% ($n = 95$) of the 121 included individuals. The genotypes did not deviate from the Hardy-Weinberg equilibrium (rs738409, $P = 0.11$; and rs58542926. $P = 0.99$), and the minor allele frequency was 18.4% (G allele) for rs738409 and 6.3% (T allele) for rs58542926. In total, 28 individuals were either homozygotes (GG, $n = 7$) or heterozygotes (CG, $n = 21$) for the minor G allele of PNPLA3 rs738409, and the minor allele frequency was 32.1% among case subjects and 16.1% among control subjects. Using an additive model resulted in an odds ratio (OR) for NAFL of 2.48 ($P = 0.06$). Concerning *TM6SF2* rs58542926, none of the participants was homozygous (TT) for the minor T allele, 12 individuals were heterozygous (TC), and none of them was in the group with NAFL. Because the number of participants carrying the T allele was limited, the SNP was excluded from further analyses. The distribution of individuals with the SNPs rs738409 and rs58542926 according to the presence of NAFL is depicted in Table 1.

Individuals with NAFL had a longer duration of diabetes and higher HbA_{1c} and triglycerides than those without NAFL. Moreover, they had lower insulin sensitivity based on the lower eGDR (3.1 mg/kg/min vs. 7.6 mg/kg/min, $P < 0.001$) and higher daily insulin requirement per kilogram of body weight (0.76 IU/kg vs. 0.52 IU/kg, $P = 0.026$) (Table 1). More people in the NAFL group were centrally obese (85.7% vs. 45.8%, $P = 0.005$) compared with the group without NAFL. Interestingly, the percentage of total, appendicular, or gynoid adipose tissues did not differ between the individuals with or without NAFL (Table 2). Nevertheless, those with NAFL presented with higher percentages of android (3.47% vs. 2.40%, $P = 0.02$) and visceral (1.83% vs. 0.55%, $P = 0.01$) adipose tissues compared with control subjects without NAFL (Table 2).

By using logistic regression models to explore whether the compartments of body adipose tissues are associated with NAFL, we found that the volume and percentage of visceral adipose tissue were positively associated with NAFL not only in the unadjusted model but also after adjusting for covariates (Table 3). In the unadjusted model, for each 1% increase in visceral adipose tissue, the odds of NAFL increased 4.6-fold ($P = 0.001$) (Table 3). However, the percentages of appendicular, gynoid, and total adipose tissues were not associated with NAFL (Table 3).

We used logistic regression models to evaluate the association between WHtR, BMI, and NAFL. Similarly to the visceral adipose tissue, the increase in WHtR was positively associated with NAFL in the unadjusted model (OR 7.59, $P < 0.001$), and this association remained after adjusting for sex, age, and duration of diabetes (OR 7.50, $P = 1.40 \times 10^{-4}$) and additional adjustments for HbA_{1c} (OR 6.68, $P = 4.47 \times 10^{-4}$), triglycerides (OR 5.12, $P = 0.003$), or the *PNPLA3* SNP rs738409 (OR 6.64, $P < 0.001$). BMI

Table 1—Clinical characteristics and genetic data of participants according to NAFL

	NAFL (−)	NAFL (+)	*P* value
n (%)	107 (88.4)	14 (11.6)	
Women	54.2	35.7	0.19
Age (year)	37.8 (32.6–43.3)	42.8 (31.4–46.7)	0.23
Age at onset diabetes (year)	14.2 (8.6–22.8)	8.1 (4.8–25.0)	0.11
Duration of diabetes (year)	20.6 (17.7–27.3)	27.8 (19.6–32.7)	0.049
Systolic blood pressure (mmHg)	129 ± 14	135 ± 17	0.16
Diastolic blood pressure (mmHg)	77 ± 9	82 ± 11	0.06
Total cholesterol (mmol/L)	4.34 (3.96–4.91)	4.65 (3.76–5.80)	0.35
HDL-cholesterol (mmol/L)	1.47 ± 0.36	1.34 ± 0.44	0.20
LDL-cholesterol (mmol/L)	2.60 (2.27–3.18)	2.84 (2.17–4.04)	0.47
Triglycerides (mmol/L)	0.86 (0.70–1.20)	2.05 (1.13–2.60)	<0.001
hs-CRP (mg/L)	1.22 (0.49–3.03)	3.84 (1.34–7.81)	0.002
HbA_{1c} (mmol/L)	63.9 ± 12.7	74.9 ± 9.8	0.002
HbA_{1c} (%)	8.0 ± 1.2	9.0 ± 0.9	0.002
Daily insulin (IU/kg body weight)	0.52 (0.39–0.66)	0.75 (0.50–0.91)	0.026
eGDR (mg/kg/min)	7.6 (4.8–9.2)	3.1 (2.1–4.5)	<0.001
Liver fat fraction (%)	0.8 (0.0–3.9)	10.5 (6.7–11.8)	<0.001
Alcohol consumption (g/day)	8.6 (3.4–16.3)	6.9 (0.0–12.9)	0.24
eGFR (mL/min/1.73 m^2)	109 (98–116)	112 (105–122)	0.22
Anthropometric measures			
Weight (kg)	80.4 ± 14.2	92.5 ± 24.3	0.09
Height (cm)	174.1 ± 9.7	172.3 ± 9.8	0.52
BMI (kg/m^2)	26.5 ± 4.0	30.8 ± 6.3	0.024
Waist (cm)	87.7 ± 10.8	105.1 ± 18.9	0.005
Waist-to-hip ratio	0.86 ± 0.07	0.98 ± 0.08	<0.001
WHtR	0.49 (0.47–0.55)	0.60 (0.53–0.68)	<0.001
WHtR ≥0.5	45.8	85.7	0.005
Genetics	*n* = 81	*n* = 14	
PNPLA3			0.09
CC	72.8	57.2	
CG	22.2	21.4	
GG	5.0	21.4	
TM6SF2			0.20
CC	85.2	100	
TC	14.8	00	
TT	00	00	

Data are shown as percentages for categorical variables, median (interquartile range) for nonnormally distributed continuous variables, and mean ± SD for continuous variables with normal distribution. Between-group comparisons were done with the χ^2 test or the Fisher exact test when the cells had an expected number <5, Mann Whitney *U* test, and independent samples *t* test, respectively. In the NAFL(−) group, 50 of 107 individuals were missing alcohol consumption data.

was associated with NAFL (OR 1.21, $P = 0.002$) in the unadjusted model, after adjusting for sex, age, and duration of diabetes (OR 1.22, $P = 0.004$) and additional adjustments for HbA_{1c} (OR 1.19, $P = 0.015$), triglycerides (OR 1.16, $P = 0.045$), or the *PNPLA3* SNP rs738409 (OR 1.22, $P = 0.004$). According to the ROC curve, we found that the commonly used WHtR threshold of 0.5 was the best cutoff to detect NAFL in this population, with an 86% sensitivity and 55% specificity. The BMI of 26.6 kg/m^2 was the best cutoff, with a 79% sensitivity and 57% specificity. The well-known BMI cutoff of 25 kg/m^2 showed a sensitivity of 86% and specificity of 43%, whereas the BMI of 30 kg/m^2 showed a 43% sensitivity and 81% specificity. The AUC of the association between WHtR and NAFL (0.823 [95% CI 0.692–0.955], $P < 0.001$) was larger ($P = 0.04$) than the AUC of the association between BMI and NAFL (0.720 [95% CI 0.572–0.955], $P < 0.007$) (Fig. 1).

CONCLUSIONS

The main finding of this study is that the visceral adipose tissue, but not the total or the peripheral body fat (appendicular and gynoid adipose tissues), is associated with NAFL in adults with type 1 diabetes. Furthermore, we showed that WHtR, a simple and low-cost surrogate marker of visceral adipose tissue, is strongly associated with NAFL and could be used as a screening tool for NAFL in this population.

Although NAFL has often been linked to obesity in the general population and in individuals with type 2 diabetes (1,28), its presence in individuals with type 1 diabetes is not negligible. A previous study in individuals with type 1 diabetes showed a prevalence of up to 50% of NAFL when assessed by ultrasound (10). This number is considerably higher than the 11.6% prevalence found in our cohort or in two other studies in which MRI was used to assess the liver fat content (9,11). The differences in prevalence are most likely explained by the different methods used to measure the liver fat content (21). The prevalence of NAFL found in our study was lower than the prevalence of NAFL in type 2 diabetes or the general population (1,11), possibly because individuals with type 1 diabetes do not have insulin delivery from the pancreas into the portal system acting directly on the liver insulin receptors and thereby stimulating lipogenesis (7). In line with this hypothesis is the 8.8% prevalence of NAFL in American individuals with type 1 diabetes compared with 75.6% of Americans with type 2 diabetes as shown in the American study by Cusi et al. (11), whereas the prevalence of NAFL in the American general population varies from 19 to 46% (1,11).

In the current study, the individuals with NAFL showed more signs of chronic inflammation (higher serum hs-CRP) and insulin resistance (lower eGDR and higher daily insulin requirement per kilogram of body weight), suggesting that these individuals may have NAFLD, which encompass insulin resistance and inflammation beyond steatosis. The harmful consequences of NAFLD go beyond the liver and are associated with

Table 2—Body composition of participants according to NAFL

Body composition	NAFL (−) $n = 74$	NAFL (+) $n = 10$	*P* value
Total adipose tissue (kg)	24.50 ± 8.75	28.88 ± 10.50	0.15
Total adipose tissue (%)	31.31 ± 8.52	33.93 ± 6.78	0.35
Appendicular adipose tissue (kg)	11.05 ± 4.00	10.80 ± 3.06	0.85
Appendicular adipose tissue (%)	14.32 ± 4.54	12.97 ± 2.19	0.14
Gynoid adipose tissue (kg)	4.35 (3.18–5.09)	3.89 (3.16–4.94)	0.76
Gynoid adipose tissue (%)	5.75 (3.91–6.94)	5.13 (4.48–5.31)	0.30
Android adipose tissue (kg)	1.90 (1.38–2.48)	3.04 (1.45–4.06)	0.033
Android adipose tissue (%)	2.40 (1.99–3.08)	3.47 (2.35–4.53)	0.023
Visceral adipose tissue (kg)	0.43 (0.18–0.99)	1.60 (0.26–3.02)	0.013
Visceral adipose tissue (%)	0.55 (0.25–1.13)	1.83 (0.41–3.03)	0.012
Visceral adipose tissue (cm^3)	452 (186–1055)	1693 (279–3196)	0.013

Data are shown as median (interquartile range) for nonnormally distributed variables and mean ± SD for variables with normal distribution. Between-group comparisons were done with the Mann Whitney *U* test and independent samples *t* test, respectively. Appendicular means both arms and legs. The percentages of body composition are related to total body weight.

cardiovascular disease in the general population, in type 2 diabetes (12,28), and also in people with type 1 diabetes (13). However, the answer to the question of whether the low-grade chronic inflammation together with the lower insulin sensitivity found in our study contributes to the progression of NAFL and/or cardiovascular outcomes requires future longitudinal studies.

The inflammatory status and low insulin sensitivity found in our population are possibly a consequence of the higher volume and percentage of visceral adipose tissue in those with NAFL compared with those without, given that an increase in visceral adipose tissue is closely associated with chronic inflammation and insulin resistance (19,29).

In the current study, we observed that the associations between the visceral adipose tissue and the NAFL were still significant after adjusting for age, sex, duration of diabetes, $HbA_{1c,}$ or triglycerides. In addition, we explored whether genetics could be a confounder, since the SNP rs738409 in *PNPLA3* has been linked to NAFL (1,14). The visceral adipose tissue was associated with NAFL even after adjusting for sex, age, duration of diabetes, and the SNP. Furthermore, a similar association by using unadjusted and adjusted models was seen between NAFL and WHtR, which is a surrogate marker of visceral adipose tissue (30). Interestingly, the liver fat accumulation associated with the SNP is not linked to insulin resistance (15,16), but the individuals with NAFL in our cohort presented with lower insulin sensitivity than those without NAFL, suggesting that NAFL may be a consequence of excess of visceral adipose tissue rather than genetics.

In contrast to a previous publication (31), our results suggest that individuals with type 1 diabetes are not protected from NAFL just because they do not have portal insulin acting directly on the liver insulin receptors and activating the glycogen synthesis and de novo lipogenesis (7). However, peripheral insulin indirectly regulates the hepatic glucose and lipid metabolism by inhibiting adipose lipolysis and promoting muscle glucose uptake (7). Therefore, individuals with type 1 diabetes may accumulate fat in the liver as long as they are centrally obese and insulin resistant. On the other hand, the increased fat deposition in the liver can also lead to insulin resistance in the liver, which in turn would increase the hepatic glucose output, contribute to hyperglycemia and dyslipidemia (6,7), and thereby maintain the cycle of insulin resistance and metabolic disturbances.

We also found that the total and peripheral body fat were not associated with NAFL. Notably, these findings reflect the different metabolic functions of the adipocytes in different adipose tissue compartments, such as visceral and subcutaneous adipose tissues (32,33). Another example of the differences between adipose tissue compartments concerns the android adipose tissue, which is composed of visceral and subcutaneous adipose tissues located in the central region of the body. In the current study, the android adipose tissue was associated with NAFL in the unadjusted model and after adjusting for age, sex, and duration of diabetes, but not after adjusting for HbA_{1c}, triglycerides, or the SNP rs738409 in *PNPLA3*. On the other hand, the visceral adipose tissue was still associated with NAFL after all adjustments, suggesting the visceral adipose tissue is crucial for the accumulation of fat in the liver. The impact of the android adipose tissue on NAFL was probably attenuated by the presence of subcutaneous fat.

Although peripheral body fat has been proposed as a protective adipose tissue concerning metabolic diseases (6,33), in our study, it was not protective of NAFL. The individuals with NAFL presented similar percentages of appendicular and gynoid adipose tissues but higher percentages of visceral and android adipose tissues than those without NAFL, which means that the central fat distribution is possibly behind the results. The higher prevalence of central obesity in individuals with NAFL could also be related to sex. However, there was no difference in sex distribution between the two groups. Additionally, we included sex as a covariate in all models of the logistic regression to mitigate this issue.

Table 3—Associations between body fat distribution and NAFL

	Model 1		Model 2		Model 3		Model 4		Model 5	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
TAT (%)	1.04 (0.96–1.13)	0.35	1.07 (0.95–1.21)	0.24	1.09 (0.96–1.23)	0.18	1.01 (0.89–1.15)	0.86	1.07 (0.95–1.22)	0.27
AppAT (%)	0.93 (0.79–1.09)	0.36	0.93 (0.70–1.22)	0.58	0.98 (0.71–1.34)	0.89	0.94 (0.70–1.25)	0.66	0.93 (0.69–1.24)	0.61
GAT (%)	0.83 (0.56–1.24)	0.36	0.74 (0.36–1.52)	0.41	0.86 (0.38–1.97)	0.73	0.70 (0.32–1.54)	0.38	0.78 (0.36–1.66)	0.51
AAT (%)	2.41 (1.22–4.74)	0.01	2.34 (1.04–5.28)	0.04	2.36 (1.00–5.53)	0.04	1.60 (0.65–3.95)	0.31	2.05 (0.93–4.54)	0.07
VAT (%)	4.63 (1.83–11.67)	0.001	4.77 (1.46–15.57)	0.01	4.17 (1.12–15.51)	0.03	3.88 (0.98–15.37)	0.05	4.09 (1.22–13.74)	0.02
VAT (cm^3)	1.001 (1.001–1.002)	0.001	1.001 (1.000–1.003)	0.01	1.001 (1.000–1.003)	0.03	1.001 (1.000–1.003)	0.04	1.001 (1.000–1.002)	0.03

Associations were calculated using a binary logistic regression model with NAFL as the outcome. Model 1 was unadjusted; model 2 was adjusted for unmodifiable risk factors such as age, sex and duration of diabetes; model 3 was adjusted for unmodifiable risk factors plus HbA_{1c}; model 4 was adjusted for unmodifiable risk factors plus triglycerides; and model 5 was adjusted for unmodifiable risk factors plus rs738409 in *PNPLA3*. AAT, android adipose tissue; AppAT, appendicular adipose tissue; GAT, gynoid adipose tissue; TAT, total adipose tissue; VAT, visceral adipose tissue.

The reason why some individuals with central obesity develop NAFL, and some do not, is still unclear and cannot be answered by our cross-sectional study. However, the interactions between genetic variants and body fat distribution (34,35) and liver fat accumulation (14) is a possible hypothesis to be investigated in future studies.

Finally, considering that the assessment of visceral adipose tissue requires costly imaging procedures such as DXA, we showed in this study that a simple measure such as the WHtR is strongly associated with NAFL and may assist in screening individuals with type 1 diabetes at higher risk of NAFL for further referral to imaging evaluation. This is in line with results in the general Finnish population in which the WHtR showed a hazard ratio of 1.44 (95% CI 1.12–1.87) for the incidence of NAFLD (36). The AUC of the ROC curve for the association between WHtR and NAFL in our cohort was 0.823 (95% CI 0.692–0.955), which is similar to a previous publication including individuals without diabetes (AUC 0.878 [95% CI 0.82–0.94]). These findings suggest that WHtR is a reliable tool for screening NAFL (37). Furthermore, according to our results, the WHtR and BMI measures were both associated with NAFL. However, WHtR showed a stronger association with NAFL than BMI, which is in line with the association between central body fat and NAFL but not between peripheral body fat and NAFL. If BMI were to be used as a screening tool, the suggested cutoff would be 26.6 kg/m^2, which showed a similar specificity compared with the WHtR cutoff of 0.5, although with lower sensitivity.

A limitation of the current study is the absence of serum hepatic enzymes and platelets, which would have enabled the calculation of a clinical score of fibrosis, as well as the estimation of hepatocyte injury. However, the lack of this information did not impact our results because we aimed to study the association between body fat distribution and NAFL, not nonalcoholic steatohepatitis. The lack of dietary and physical activity information is a shortcoming because the diet components could have had an impact on NAFL and the body composition. Finally, the cross-sectional study limits any inferences to causal relationships.

Nevertheless, the study has several strengths. The individuals were thoroughly examined, and the liver fat content was measured by MRI and the body composition by DXA, which are gold standard methods. Another strength is that the SNPs rs738409 in *PNPLA3* and *TM6SF2* rs58542926 were available as directly genotyped SNPs in the genome-wide association study with no missing data for 95 of the 121 study participants. Overall, our results motivate further studies to explore possible mechanisms and genetic variants involved in the relationship between body fat distribution and ectopic fat deposits in the liver of people with type 1 diabetes.

From a clinical point of view, beyond showing that the visceral adipose tissue is associated with NAFL in adults with type 1 diabetes, we also show that WHtR may be useful as an easy and inexpensive tool to screen individuals at higher risk of NAFL. Then, future studies will show the cost-effectiveness of this tool. Finally, considering the recent publication regarding the effect of liraglutide on the reduction of adipose tissue and visceral fat in type 1 diabetes (38), our results raise a question to be answered by future clinical trials whether individuals with type 1 diabetes, central obesity, and NAFL should receive pharmacological treatment for obesity and insulin resistance beyond lifestyle recommendations and insulin therapy.

In conclusion, our study shows that individuals with type 1 diabetes are not protected from NAFL and that visceral adipose tissue is associated with NAFL after adjusting for confounders, including the missense SNP rs738409 in the *PNPLA3* gene. Furthermore, the WHtR may be considered as a screening tool for NAFL in this population.

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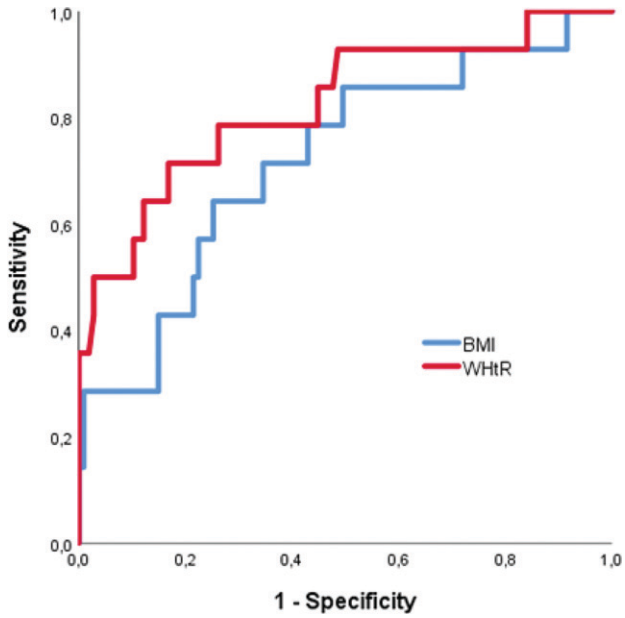

Figure 1—ROC curve of WHtR, BMI, and the presence of NAFL. WHtR AUC: 0.823 (95% CI 0.692–0.955) vs. BMI AUC: 0.720 (95% CI 0.572–0.955), $P = 0.04$.

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Author Contributions. E.B.P. and P.-H.G. were responsible for the concept and study design. E.B.P was responsible for the statistical analyses, and preparation of the manuscript. E.H.D. and N.S. were responsible for the acquisition and analysis of genetic data. V.H., C.F., S.M., and D.G. contributed to the acquisition of the clinical data. J.I. analyzed the liver MRI images. All authors interpreted the results and contributed to the critical revision of the manuscript. All authors reviewed the manuscript and approved the final version. P.H.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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