Risk of non alcoholic steatohepatitis and fibrosis in patients with non alcoholic fatty liver disease and low visceral adiposity

Risk of nonalcoholic steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease and low visceral adiposity

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Background & Aims

Increased visceral adiposity is considered the hallmark of the metabolic syndrome, whose hepatic manifestation is nonalcoholic fatty liver disease (NAFLD), although a subset of patients does not have visceral obesity. Our study aimed to compare metabolic alterations and liver damage in patients with NAFLD with and without visceral obesity.

Methods

Four hundred and thirty one consecutive patients with liver biopsy-confirmed NAFLD were divided in three groups according to waist circumference, the simplest surrogate marker of visceral obesity. One hundred and thirty three patients (31%) had a waist circumference ⩽94 (males) and ⩽80 cm (females) (group A), 157 (36%) between 94 and 102, and 80 and 88 (B), and the remaining 141 (33%) had values higher than 102 and 88 cm (C).

Results

Significant trends for older age, higher prevalence of female gender, lower HDL, higher triglycerides, altered glucose metabolism, hypertension, and metabolic syndrome were observed with increasing visceral adiposity. In contrast, non-alcoholic steatohepatitis (NASH) detected in 55% and 72% of patients with normal and increased waist circumference, respectively, and the presence of fibrosis ⩾2 were not associated with visceral adiposity. Alanine aminotransferase (ALT), ferritin, HOMA-IR >4, and severe steatosis were independently associated with NASH, whereas ferritin and impaired glucose tolerance were associated with fibrosis ⩾2.

Conclusions

Patients with normal waist circumference, despite milder metabolic alterations, may have NASH and are at risk of developing fibrosis, suggesting that once NAFLD is present, visceral obesity is not a major determinant of liver damage severity.

Abbreviations

NAFLD, nonalcoholic fatty liver disease;

NASH, nonalcoholic steatohepatitis;

HOMA-IR, homeostatic model assessment insulin resistance index;

BMI, body mass index;

ALT, alanine aminotransferase;

GGT, gamma-glutamyltransferase;

OGTT, oral glucose tolerance test;

OR, odd ratio;

adj, adjusted;

CI, confidence intervals

Introduction

Increased visceral adiposity is considered the hallmark of the metabolic syndrome, a clinical condition characterized by increased cardiovascular risk driven by raised blood pressure, dyslipidemia, and altered glucose regulation. However, in recent years a subset of patients has been identified, with normal body weight and similar metabolic disturbances (so called metabolically-obese, normal weight (MONW) cases), who also shares a similar cardiovascular risk [1].

The various clinical expressions of nonalcoholic fatty liver disease (NAFLD), from pure fatty liver to nonalcoholic steatohepatitis (NASH), cryptogenic cirrhosis, and eventually hepatocellular carcinoma are considered a manifestation of the metabolic syndrome. Also among NAFLD cases, a subset of patients does not present with visceral obesity, but insulin resistance remains the common soil of both the metabolic syndrome and NAFLD, largely independent of increased fat mass. In a prospective study, subjects with NAFLD and elevated ALT were reported to be at higher risk of developing diabetes and the metabolic syndrome than subjects without NAFLD, and the risk was driven by waist circumference, hypertension, and insulin resistance [2].

Conflicting evidence has been reported on the complex relationship between visceral fat mass, insulin resistance and NAFLD. The severity of insulin resistance is a determinant of liver damage progression in NAFLD [3] and adipose tissue insulin resistance was recently proposed to underlie the pathogenesis of liver damage [4], [5] and [6]. Accordingly, visceral obesity might represent a non-invasive marker of disease severity in the general NAFLD population. However, adequately powered studies assessing the association between waist circumference and liver damage are not available.

Waist circumference remains the simplest and most widely used surrogate marker of visceral adiposity [7] and [8], and other proposed surrogate markers, including the recent perihepatic adipose tissue thickness at ultrasonography, skin thickness, and dorsal cervical fat are scarcely used in the clinical setting [9] and [10]. The aim of this study was to compare metabolic alterations and severity of liver damage in patients with NAFLD with and without increased visceral obesity, simply estimated by the easily available waist circumference measure, to define which are the variables associated with hepatic and extrahepatic morbidities.

Methods

Patients

We merged the databases of consecutive patients with liver biopsy-confirmed NAFLD observed in four Liver Units. All consecutive patients who underwent liver biopsy between January 2003 and June 2009 were included in the study unless the tissue sample size was <1.7 cm. The final cohort was made up of 431 cases. Most of these patients had been included in a previous multicenter Italian study [11]. Other causes of liver diseases (viral, autoimmune, cholestatic, drug-induced, hereditary hemochromatosis, Wilson's disease) were excluded. In all patients, daily alcohol intake was lower than 20 g (confirmed by at least one family member). Clinical and laboratory data were collected at the time of liver biopsy (Table 1).

Table 1.

Characteristics of patients with NAFLD, divided according to abdominal circumference (group A<94 and <80 cm, group B⩾94 <102 and ⩾80 <88, group C⩾102 and ⩾88 cm in man and woman, respectively).

Variables	Group A (n = 133)	Group B (n = 157)	Group C (n = 141)	*p* value
M/F	128/5	140/17	92/49	<0.001
Age (yrs)	39 ± 10	42 ± 11	47 ± 11	<0.001
BMI (Kg/m^2)	25 ± 2.2	27.5 ± 2.6	30.1 ± 4.1	<0.001
Total cholesterol (mg/dl)	200 ± 39	206 ± 47	207 ± 44	0.29
HDL (mg/dl)	48 ± 13	47 ± 11	45 ± 12	0.03
Triglycerides (mg/dl)	131 ± 86	152 ± 83	164 ± 84	<0.001
Fasting glucose (mg/dl)	93 ± 15	95 ± 24	105 ± 37	0.04
Fasting insulinemia (μU/ml)	14.8 ± 9.9	17.7 ± 12.7	20.8 ± 12.3	<0.001
HOMA-IR	3.4 ± 2.4	4.3 ± 5.0	5.1 ± 3.7	<0.001
ALT (U/L)	71 ± 45	80 ± 47	75 ± 47	0.2
GGT (U/L)	89 ± 104	82 ± 89	88 ± 95	0.46
Serum ferritin (ng/ml)	298 ± 250	339 ± 316	390 ± 337	0.25
Transferrin saturation (%)	35 ± 11	36 ± 12	34 ± 16	0.5
Impaired glucose tolerance	13 (9.8)	15 (9.6)	37 (26.2)	<0.001
Diabetes	7 (5.3)	11 (7.0)	22 (15.6)	0.006
Hypertension	26 (20.6)	52 (34.2)	72 (52.2)	<0.001
Metabolic syndrome	10 (7.5)	25 (15.9)	76 (53.9)	<0.001
NASH	73 (54.9)	83 (52.9)	101 (71.6)	0.002
Fibrosis stage (>2)	37 (27.8)	41 (26.1)	52 (36.9)	0.10
Steatosis grade 3	7 (5.3)	27 (17.2)	36 (25.9)	<0.001

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Mean ± SD or number of cases and (%). *p*-Values from ANOVA or chi-square test.

Patients with clinical or imaging evidence of decompensated cirrhosis were excluded from the study. Liver biopsy was performed in 323 (75%) patients because of abnormalities in liver function tests, whereas in the remaining 108 either a persistent increase in serum ferritin or a long-lasting history of steatosis was the main reason for biopsy.

All patients had given informed, written consent to data handling according to a protocol approved by the Senior Staff Committee of our Institutions, a board comparable to an Institutional Review Board.

Methods

The database contained data on life habits, clinical and pharmacological history, BMI, waist circumference (measured in a standing position at the level of the umbilicus) and arterial blood pressure (defined as the mean of the second and third reading of three consecutive blood pressure measurements), blood count, liver function tests (AST, ALT, gamma-glutamyltransferase (GGT), serum albumin, platelets count, bilirubin), fasting glucose and insulin, total and HDL cholesterol, triglycerides, and uric acid. All tests were determined by standard laboratory procedures; insulin by a commercially purchased radioimmunoassay (RIA, Biochem Immunosystems, Bologna, Italy). The upper normal limit of ALT levels was set at 40 U/L. The diagnosis of the metabolic syndrome was carried out according to ATPIII criteria [12], and based on the presence of 3 or more of the following criteria: (1) fasting glucose $\geqslant$100 mg/dl, (2) central obesity (waist circumference >102 cm (men) and >88 cm (women), (3) arterial pressure $\geqslant$130/85 mmHg or treatment for hypertension, (4) triglycerides levels $\geqslant$150 mg/dl or use of fibrates, (5) HDL-cholesterol <40 mg/dl (men) and <50 mg/dl (women).

Insulin resistance was evaluated according to the homeostatic model assessment insulin resistance index (HOMA-IR) [13], as fasting serum insulin (in µIU/ml) multiplied by fasting serum glucose (in mMol/L), divided by 22.5. Oral glucose tolerance test (OGTT) was performed with 75 g of glucose according to World Health Organization criteria in 382 (89%) patients.

The presence of diabetes mellitus (fasting glucose $\geqslant$126 mg/dl, 120-min glucose $\geqslant$200 during OGTT, or treatment with antidiabetic drugs), obesity (BMI >30 kg/m2) and overweight (BMI, 25–29.9 kg/m2) were defined using standard criteria.

Liver histology

Liver biopsies were routinely processed and read by a single pathologist in each center. To control for biopsy size, the length of the biopsy was measured with a hand ruler, and the number of portal areas on a cross-section was counted. The minimum biopsy size was 1.7 cm and the number of portal areas 10. The diagnosis of NASH was based on the pathologist's overall impression according to Brunt criteria [14], modified by Kleiner [15]. The stage of fibrosis was scored based on the 5-point scale (stage 0, absence of fibrosis; stage 1, perisinusoidal or portal fibrosis; stage 2, perisinusoidal and portal/periportal fibrosis; stage 3, septal or bridging fibrosis; stage, 4 cirrhosis). The severity of steatosis was graded from 1 to 3 according to the percentage of cells with fatty droplets (1: 6–33%, 2: 33–66%, and 3 >66%).

Statistical analysis

Results are expressed as means ± standard deviations for continuous variables and as frequencies for categorical variables. p-Values from ANOVA or chi-square test were considered statistically significant if $\leqslant 0.05$. Logistic regression analyses were performed to calculate odds ratios (OR), and their 95% confidence intervals (CI) for two outcomes, NASH, and fibrosis grade $\geqslant 2$ (the latter value was chosen because of the relatively mild fibrosis detected in our series) [11]. Variables significant at univariate analyses or of a priori interest were entered into the final multivariate model. Independent variables were categorized according to quartiles (ALT), tertiles (ferritin), or following commonly used cut-offs. In particular, waist circumference was categorized in three groups, (group A <94 and <80 cm, group B $\geqslant$94 <102 and $\geqslant$80 <88, group C $\geqslant$102 and $\geqslant$88 cm in man and woman, respectively) [12] and [16]; steatosis was graded from 1 to 3 [11]. Age was divided in decades, and HOMA-IR categories were arbitrarily chosen as follows: <2.5, absence of insulin resistance; 2.5–4.0, moderate insulin resistance; >4, severe insulin resistance. p-Values for linear trends were calculated for ordinal variables. All statistical analyses were performed with the Stata 11 software [17].

Results

The characteristics of patients subdivided in three groups according to waist circumference are shown in Table 1. At increasing waist circumference, patients were progressively older, and more frequently of female gender, had a higher BMI, lower HDL-cholesterol, higher triglycerides, and higher fasting glucose, insulin, and HOMA-IR. In addition, there was an increased prevalence of impaired glucose tolerance and diabetes, arterial hypertension, and metabolic syndrome, which paralleled the increase in visceral obesity.

The prevalence of severe steatosis and NASH increased with higher waist circumference, whereas the prevalence of severe fibrosis was not significantly associated with waist girth. At multivariate analysis, after adjustment for referral center, NASH and fibrosis were not significantly associated with waist

circumference evaluated either as a categorized or as a continuous variable. The variables independently associated with NASH were ALT levels, serum ferritin and HOMA-IR in the upper tertile, and steatosis grade 3 (Table 2); those associated with fibrosis ⩾2 (Table 3) were serum ferritin >380 ng/ml and impaired glucose tolerance.

Table 2.

Risk of NASH according to selected clinical variables.

Variables	No NASH (n = 174) n (%)	NASH (n = 257) n (%)	OR	95% C.I.	OR
Gender					
M	152 (42.2)	208 (57.8)	1.00*		1.0
F	22 (31.0)	49 (69.0)	1.63	0.94-2.81	1.5
Age (yrs)					
<30	21(42.8)	28 (57.2)	1.00*		1.0
30-39	60 (45.1)	73 (54.9)	0.91	0.47-1.77	1.1
40-49	46 (39.7)	70 (60.3)	1.14	0.58-2.24	1.4
50-59	32 (34.8)	60 (65.2)	1.41	0.69-2.86	1.4
≥60	15 (36.6)	26 (63.4)	1.30	0.55-3.04	0.9
p for trend			0.15	0.95-1.33	0.7
Waist circumference (cm)					
<94 and 80	60 (45.1)	73 (54.9)	1.00*		1.0
>94<102 and>80<88	74 (47.1)	83 (53.9)	0.92	0.57-1.46	0.5
>102 and >88	40 (28.4)	101 (71.6)	2.07	1.25-3.42	1.2
p for trend			0.004	1.17-1.82	0.7
ALT (U/L)					
<45	49 (54.4)	41(45.6)	1.00*		1.0
46-65	57 (44.2)	72 (55.8)	1.51	0.88-2.59	1.7
66-91	32 (33.7)	63 (66.3)	2.35	1.30-4.26	1.9
91+	35 (30.2)	81 (69.8)	2.77	1.56-4.91	2.2
p for trend			0.0001	1.18-1.69	0.0
Serum ferritin (ng/ml)					
<160	57 (43.2)	75 (56.8)	1.00*		1.0
161-380	58 (40.0)	78 (60.0)	1.14	0.7-1.87	1.0
380+	38 (29.1)	93 (70.9)	1.86	1.11-3.10	2.0
p for trend			0.018	1.05-1.74	0.0
HOMA-IR					
<2.5	56 (48.7)	59 (51.3)	1.00*		1.0
2.5-4.0	61 (45.5)	73 (54.5)	1.13	0.68-1.87	1.7
4.0+	39 (29.3)	94 (70.7)	2.28	1.35-3.85	2.4
p for trend			0.002	1.16-1-95	0.0
Glucose tolerance					
Normal	149 (47.1)	177 (54.2)	1.00*		1.0
Impaired	15 (23.1)	50 (76.9)	2.8	1.5-5.19	1.0
Diabetes	10 (25.0)	30 (75.0)	2.5	1.18-5.33	0.9
p for trend			0.0001	1.32-2.64	0.9
Metabolic syndrome					
No	143 (44.7)	177 (55.3)	1.00*		1.0
Yes	31(27.9)	80 (72.1)	2.08	1.30-3.33	1.2
Steatosis					
Grade 1	103 (47.1)	116 (52.9)	1.00*		1.0
Grade 2	57 (40.7)	83 (59.3)	1.29	0.84-2.88	2.4
Grade 3	13 (18.6)	57 (81.4)	3.89	2.01-7.51	4.1
p for trend			0.0001	1.31-2.29	0.0

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*Each variable adjusted for the others in the table and for center.

Table 3.

Risk of severe fibrosis according to selected clinical variables.

Variables	Fibrosis 0-1 (n = 301) n (%)	Fibrosis 2 (n = 130) n (%)	OR	95% C.I.	OR
Gender					
M	262 (72.8)	98 (27.2)	1.00*		1.0
F	39 (54.9)	32 (4.25)	2.19	1.3-3.69	1.8
Age (yrs)					
<30	35 (71.4)	14 (28.6)	1.00*		1.0
30-39	99 (74.4)	34 (25.6)	0.86	0.41-1.78	1.3
40-49	80 (68.9)	36 (31.1)	1.12	0.54-2.34	1.8
50-59	62 (67.4)	30 (32.6)	1.21	0.57-2.58	1.4
60	25 (61.0)	16 (39.0)	1.60	0.66-3.86	1.0
p for trend			0.12	0.96-1.37	0.7
Waist circumference (cm)					
<94 and 80	96 (72.2)	37 (27.8)	1.00*		
>94<102 and>80<88	116 (73.9)	41 (26.1)	0.91	0.54-1.54	0.7
>102 and >88	89 (63.1)	52 (36.9)	1.5	0.90-2.52	1.3
p for trend			0.1	0.96-1.61	0.4
ALT (U/L)					
<45	72 (80)	18(20)	1.00*		1.0
46-65	94 (72.9)	35 (27.1)	1.48	0.78-2.84	1.2
66-91	62 (65.3)	33 (34.7)	2.12	1.09-4.14	1.3
91+	72 (62.1)	44 (37.9)	2.44	1.29-4.62	2.0
p for trend			0.003	1.10-1.42	0.1
Serum ferritin (ng/ml)					
<160	98 (74.3)	34 (25.7)	1.00*		1.0
161-380	87 (66.9)	43 (33.1)	1.42	0.83-2.43	1.6
380+	88 (67.2)	43 (32.8)	1.40	0.82-2.40	3.3
p for trend			0.21	0.90-1.23	0.0
HOMA-IR					
<2.5	87 (75.6)	28 (24.4)	1.00*		1.0
2.5-4.0	102 (76.2)	32 (23.9)	0.97	0.54-1.7	1.2
4.0+	87 (65.4)	46 (34.6)	1.64	0.94-2.8	1.5
p for trend			0.06	0.98-1.73	0.2
Glucose tolerance					
Normal	251 (77.0)	75 (23.0)	1.00*		1.0
Impaired	29 (44.6)	36 (55.4)	4.15	2.38-7.22	2.7
Diabetes	21 (52.5)	19 (47.5)	3.02	1.54-5.92	2.4
p for trend			0.0001	1.56-2.89	0.0
Metabolic syndrome					
No	234 (73.1)	86 (26.9)	1.00*		1.0
Yes	67 (60.4)	44 (39.6)	1.78	1.13-2.81	0.9
Steatosis					
Grade 1	166 (75.8)	53 (24.2)	1.00*		1.0
Grade 2	93 (66.4)	47 (33.6)			1.0
Grade 3	42 (60.0)	28 (40.0)	2.08	1.18-3.69	1.2
p for trend			0.006	1.11-1.93	0.3

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*Each variable adjusted for the others in the table and for center.

Discussion

In this study performed in a large series of well-characterized Italian patients with histologically-proven NAFLD, we analyzed metabolic alterations and liver damage in relation to the presence of visceral obesity. Our results indicate that waist circumference, an easily available surrogate marker of visceral adiposity, was strongly correlated with metabolic alterations and severity of steatosis, but not with NASH and liver fibrosis. We conclude that not yet elucidated mechanisms, including genetic factors [18], [19], [20], [21], [22] and [23] not quantifiable by the simple measure of waist circumference, are responsible for liver disease progression in patients with NAFLD and that the risk of severe liver damage should not be underestimated in lean subjects.

In our study on subjects of Caucasian origin, we used the three values of waist circumference proposed by International agencies and observed a progressive increase in the prevalence of metabolic alterations, with increasing abdominal adiposity, in patients without visceral adiposity having milder metabolic derangements, similar to previous results [12], [16], [24] and [25].

As expected, steatosis and visceral adiposity were significantly correlated, with severe steatosis (grade 3) being much more prevalent in patients with the largest waist circumference. Although the prevalence of NASH increased with increasing waist circumference, being 55% and 72% in lean and obese subjects, respectively, no relation was observed between waist circumference and NASH at multivariate analysis.

More controversial is the relation between fibrosis and visceral obesity. In an attempt to identify the variables predictive of fibrosis, several authors have investigated a variety of markers including demographic, anthropometric, biochemical, and clinical parameters, but no conclusive results have been reached [26], [27], [28], [29], [30] and [31]. Variables related to glucose control (impaired glucose metabolism/diabetes) were more frequently identified [8], [26], [27] and [28] as predictive of fibrosis, whereas the relation of increased BMI with fibrosis was uncertain. In our series, we did not find any association between BMI, which reflects total body adiposity, and the severity of fibrosis; whereas liver cell necrosis (as detected by ALT values) and the presence of altered glucose metabolism predicted the presence of fibrosis $\geqslant 2$, as previously reported.

Noteworthy, in children with NAFLD [32], [33] and [34], waist circumference was the only component of the metabolic syndrome associated with liver fibrosis. It is possible that this reflects the lower number of

confounding factors in pediatric patients, i.e. the shorter duration of liver disease and obesity, as well as differences in unhealthy lifestyle habits, comorbidities, and drugs. Interestingly, Cheung et al. [4] reported that dorso-cervical lipohypertrophy, but not waist circumference, was associated with the severity of histology in adult NAFLD, suggesting that specific fat depots are pivotal in liver fibrosis.

Morbid obesity is a paradigm of the uncertain relation between visceral obesity and liver damage in patients with NAFLD. In a recent prospective study [35], only 15–20% of patients with grade III obesity, despite the high frequency of steatosis (80%) and marked insulin resistance, had NASH; mild fibrosis was detected in less than 25% of cases, with only 4% having fibrosis $\geqslant 2$, suggesting that factors unrelated to insulin resistance (cytokines, toxic effect of lipid molecules, gut microflora, oxidative stress, etc.) are necessary to promote liver disease progression. Progression of hepatic fibrosis was documented 5 years after bariatric surgery, despite a marked weight loss, decreased insulin resistance, improved steatosis and reduced NASH prevalence. However, since fibrosis was relatively mild in obese patients submitted to bariatric surgery as well as in our patients with NAFLD [11], it remains to be defined whether the correlation with visceral adiposity changes in relation to the stage of fibrosis.

A role of adipose tissue insulin resistance has recently been proposed to explain the pathogenesis and the progression of histological liver damage in lean and obese patients with NASH [36], but it is not defined which adipose tissue is the culprit. For example, pericardial fat is more tightly associated with early coronary artery disease than waist circumference [37]. Whether specific subcomponents of body fat recently defined as ectopic fat [38], and not quantifiable by waist circumference, are involved in liver damage progression, remains to be defined.

Interestingly, a third-world NAFLD phenotype has recently been described in which subtle values of increased adiposity, not overt adiposity, predispose to NAFLD [39]. This finding could open new perspectives to understand the origin of NAFLD in lean subjects.

It is possible that genetic factors predisposing to adipose tissue dysfunction may be involved in the pathogenesis of IR in relatively lean patients who develop NAFLD and progressive liver disease.

However, we did not find an over-representation of genetic factors that we previously demonstrated to influence either IR (ENPP1 and IRS-1 polymorphisms [21]) or the severity of steatosis (PNPLA3 polymorphisms [22]), and, consequently, the severity of liver damage in relatively “lean” compared to obese patients with NAFLD, except for a decreased prevalence in patients from UK. Interestingly, the C282Y mutation in the HFE gene, associated with mild iron overload in patients with NALFD, was more frequent in lean than in obese subjects [40] and [41], suggesting that a mild increase in liver iron may lead to

augmented lipotoxicity of the fat accumulated in the liver or alter adipocytes function. However, the results of additional ongoing studies are required to clarify this issue, and it should be noted that the majority of genetic factors possibly involved is presently still unknown.

In conclusion, visceral adiposity influences the manifestations of the metabolic syndrome but not the severity of liver damage in patients with NAFLD. As a consequence, also lean patients with NAFLD, despite an apparently milder metabolic involvement, should be carefully screened and monitored for the presence of NASH and severe liver fibrosis.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Supplementary data

Supplementary Table.

Supplementary table. Prevalence of genetic factors previously associated with susceptibility to progressive liver fibrosis in patients with NAFLD with increased adiposity (waist circumference >102 cm and > 88 cm in male and female respectively or BMI>27.5 if waist circumference not

available) and normal adiposity (waist circumference <102 cm and > 88 cm in male and female respectively or BMI<27.5).

Genetic variant	Paper	Patients evaluated	Prevalence of genetic variant		p
			Increased adiposity	Normal adiposity	
HFE C282Y	Valenti, Fracanzani, et al; Gastroenterology 2010, [40]	587	19/307 (6.2%)	30/280 (10.8%)	0.053
HFE H63D	Valenti, Fracanzani, et al; Gastroenterology 2010, [40]	587	96/307 (31.3%)	90/280 (32.1%)	ns
Beta globin mutations	Valenti, Canavesi, et al; J Hepatol 2010, [42]	274	10/114 (8.1%)	15/148 (10.1%)	ns
IRS-1 G972R Italy	Dongiovanni, Valenti, et al; Gut 2010, [21]	239	22/112 (19.2%)	28/127 (22.0 %)	ns
IRS-1 G972R UK	Dongiovanni, Valenti, et al; Gut 2010, [21]	328	31/304 (10.3%)	0/24	ns
ENPP1 K121Q Italy	Dongiovanni, Valenti, et al; Gut 2010, [21]	239	21/112 (28.9%)	31/127 (24.4%)	ns
ENPP1 K121Q UK	Dongiovanni, Valenti, et al; Gut 2010, [21]	328	88/304 (29.0%)	1/24 (4.2%)	0.007
PNPLA3 I148M	Valenti, Al-Serri, et al; Hepatology 2010, [22]	592	200/459 (43.1%)	55/133 (41.4%)	ns

Ns: not significant.

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Prevalence of genetic factors previously associated with susceptibility to progressive liver fibrosis in patients with NAFLD with increased adiposity (waist circumference >102 and >88 cm in male and female respectively or BMI >27.5 if waist circumference not available) and normal adiposity (waist circumference <102 and >88 cm in male and female respectively or BMI <27.5).

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